CARE™ PERSPECTIVES
ESMO 2019
PROSTATE CANCER FOCUS

EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY
BARCELONA, SPAIN - SEPTEMBER 27 - OCTOBER 1, 2019
Throughout 2020, this milestone will be considered. Focus will be on retrospective reviews on innovation and looking forward statements for 2020 and beyond.
Introduction

2018 and 2019 have seen numerous data updates and news that can affect the management of prostate cancer (PC) in Canada.

The CARE™ Genitourinary (GU) Faculty focuses on framing potentially practice changing GU updates from a Canadian perspective.

The following CARE™ Conference Report from ESMO 2019 focuses on prostate cancer updates and includes content on:

- Metastatic castrate resistant prostate cancer (mCRPC).
- Hormone sensitive prostate cancer (HSPC - term used interchangeably with castrate sensitive prostate cancer or CSPC).
- Drug-drug interactions (DDIs).
- A novel androgen receptor inhibitor for nmCRPC (non-metastatic CRPC) and mCSPC.

To access this CARE™ Conference Report from ESMO 2019 and other Educational Outputs from the CARE™ Faculty, visit: www.CAREeducation.ca

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CARE™ SPOTLIGHT ON: A NOVEL ANDROGEN RECEPTOR INHIBITOR FOR nmCRPC AND mCSPC 09
Maha Hussain et al.

**Results:** 4425 men were screened; 245 randomized to Cohort A, 142 to Cohort B (65.6% had prior taxane). Efficacy is shown in Table 1. Most common adverse events (AEs) were anaemia (46.1 v 15.4%), nausea (41.4 v 19.2%), decreased appetite (30.1 v 17.7%) and fatigue (26.2 v 20.8%) for ola vs pcNHA; 16.4 and 8.5% of pts, respectively, discontinued due to AE.

<table>
<thead>
<tr>
<th>Table 1: LBA12_PR Efficacy summary*</th>
<th>Cohort A (alterations in BRCA1, BRCA2, or ATM)</th>
<th>Cohorts A+B (alterations in any qualifying HRR gene)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olaparib N = 162</strong></td>
<td><strong>pcNHA N = 83</strong></td>
<td><strong>Olaparib N = 256</strong></td>
</tr>
<tr>
<td>rPFS (RECIST v1.1 + PCWG3 by BICR)</td>
<td>Median, months</td>
<td>7.39</td>
</tr>
<tr>
<td>% progression-free at 12 months</td>
<td>28.11</td>
<td>9.40</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.34 (0.25 to 0.47)</td>
<td>0.49 (0.38 to 0.63)</td>
</tr>
<tr>
<td>P value</td>
<td>0.0001</td>
<td>0.0006 (nominal)</td>
</tr>
<tr>
<td>Confirmed ORR (RECIST v1.1 + PCWG3 by BICR)*</td>
<td>%</td>
<td>33.3</td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td>20.86 (4.18 to 379.18)</td>
<td>5.93 (2.01 to 25.40)</td>
</tr>
<tr>
<td>Time to pain progression</td>
<td>Median, months</td>
<td>NR</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.44 (0.22 to 0.91)</td>
<td>0.64 (0.35 to 1.21)</td>
</tr>
<tr>
<td>P value</td>
<td>0.64 (0.43 to 0.97)</td>
<td>0.67 (0.49 to 0.93)</td>
</tr>
<tr>
<td>OS (interim)†</td>
<td>Median, months</td>
<td>18.50</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.64 (0.43 to 0.97)</td>
<td>0.67 (0.49 to 0.93)</td>
</tr>
</tbody>
</table>

NR, not reached; ORR, objective response rate; OS, overall survival

* Key secondary endpoints were confirmed ORR in Cohort A, rPFS in Cohort A+B, time to pain progression in Cohort A and OS in Cohort A;
† In patients with measurable disease;
‡ Interim analysis at 38% (Cohort A) and 41% (Cohort A+B) data maturity; Of the pcNHA patients whose disease progressed by BICR and were eligible, 80.6% in Cohort A and 84.6% in Cohort B crossed over to olaparib treatment;
¥ Alpha spend at interim was 0.01; statistical significance not reached

**Conclusions:** In pts with mCRPC and HRR alterations with prior NHA treatment, ola improved rPFS and ORR vs pcNHA, with a favourable trend for OS despite crossover. Safety was generally consistent with the known profile of ola. PROfound is the first positive phase III biomarker-selected study evaluating a targeted treatment in pts with mCRPC.
CARE™ FACULTY SUMMARY AND PERSPECTIVES:

- Poly (ADP-ribose) polymerase (PARP) inhibitors are a class of targeted agent that was developed for the treatment of homologous recombination repair (HRR) deficient tumors. Studies have supported the concept that loss of function alterations in HRR genes are associated with response to PARP therapy (Hodgson et al. BJC. 2018).

- The Presidential Symposium III of ESMO 2019 included a presentation on the PROfound study which seeks to answer the question of whether olaparib (a PARP inhibitor) is active in patients with different DNA repair deficiencies.

- PROfound utilized 2 patient cohorts:
  - Cohort A: Patients with alterations in BRCA1, BRCA2 or ATM.
  - Cohort B: Patients with any 1 of 12 other HRR alterations (BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L).

- PROfound demonstrated that patients with BRCA1, BRCA2 or ATM mutations who are taking olaparib have a prolonged time to radiographic progression (7.39 months) compared to patients receiving abiraterone acetate or enzalutamide (3.55 months).

- The results of PROfound also displayed a favorable OS trend for patients receiving olaparib despite a crossover (approximately 70% of patients in the control arm received olaparib at progression). Additionally, the majority of the toxicities observed in patients on olaparib were mild and manageable.

- This is the first phase 3 trial in mCRPC to show that a targeted drug, administered to pre-selected patients based on genetic and genomic background may be efficacious - these results exhibit a trend towards personalized mCRPC management.

- The ability to distinguish certain genetic alterations (e.g. BRCA1, BRCA2 and ATM) in PC patients will be a challenge for Canadians as genetic testing is not universally available or administered to all prostate cancer patients. If available, genetic tests for PC patients could help physicians sequence therapies and make management decisions, similar to the role of genetics in breast or ovarian cancers.

PROfound DEMONSTRATED THAT PATIENTS WITH BRCA1, BRCA2 OR ATM MUTATIONS WHO ARE TAKING OLAPARIB HAVE A PROLONGED TIME TO RADIOGRAPHIC PROGRESSION (7.39 MONTHS) COMPARED TO PATIENTS RECEIVING ABIRATERONE ACETATE OR ENZALUTAMIDE (3.55 MONTHS).

PAGE: 02
LBA13 - CARD: Randomized, open-label study of cabazitaxel (CBZ) vs abiraterone (ABI) or enzalutamide (ENZ) in metastatic castration-resistant prostate cancer (mCRPC)

Ronald De Wit et al.

Results: Overall, 255 patients (median age 70, 31.0% ≥ 75 yrs) were randomized. Median number of cycles was higher for CBZ vs ART (7 vs 4). rPFS was significantly improved with CBZ vs ART (median 8.0 vs 3.7 mo; HR 0.54; 95% CI 0.40–0.73; p < 0.0001). CBZ also significantly improved OS (median 13.6 vs 11.0 mo; HR 0.64; 95% CI 0.46–0.89; p = 0.0078) despite crossover, as well as PFS (median 4.4 vs 2.7 mo; p < 0.0001), confirmed PSA50 response (35.7% vs 13.5%; p = 0.0002) and tumor response (36.5% vs 11.5%; p = 0.004). Pain response and time to symptomatic skeletal events were also significantly improved with CBZ. Grade ≥ 3 adverse events (AEs) occurred in 56.3% vs 52.4% of patients with CBZ vs ART. For CBZ vs ART, main grade ≥ 3 AEs were: renal disorders (3.2% vs 8.1%); infections (7.9% vs 7.3%); musculoskeletal pain/discomfort (1.6% vs 5.6%); cardiac disorders (0.8% vs 4.8%); spinal cord/nerve root disorders (2.4% vs 4.0%); asthenia/fatigue (4.0% vs 2.4%); diarrhea, peripheral neuropathy and febrile neutropenia (3.2% vs 0% for each). AEs led to death in 7 vs 14 patients (5.6% vs 11.3%) for CBZ vs ART.

Conclusions: CBZ significantly improved clinically important patient outcomes including rPFS and OS vs ART in patients with mCRPC previously treated with DOC and an alternative ART. CBZ should be the preferred option in this setting.

CARE™ FACULTY SUMMARY AND PERSPECTIVES:

- Current standard of care therapies for mCRPC in Canada include (second generation) androgen receptor targeted (ART) therapies such as abiraterone (abi) and enzalutamide (enza) as well as taxanes like docetaxel (DOC) and cabazitaxel (CBZ).
- Although the therapies listed above are Health Canada approved and efficacious in the mCRPC setting, questions remain regarding how these therapies can be optimally sequenced.
- In the CARD Study:
  - mCRPC patients who progressed within 12 months on either abiraterone or enzalutamide and were randomized (1:1) to either cabazitaxel or the other anti-androgen therapy (patients who previously received abi received enza, patients who previously received enza received abi). Patients enrolled in the study had also received at least 3 prior cycles of docetaxel and had castration levels of testosterone.
  - The European dose of 25 mg/m² of cabazitaxel with G-CSF prophylaxis was used (different to the equally effective FDA approved dose of 20 mg/m²).

Secondary endpoints: OS, PFS and tumour response.
- In CARD, cabazitaxel treatment offered a statistically significant rPFS benefit over alternative anti-androgen therapy (median rPFS of 8.0 versus 3.7 months, HR 0.54, P < 0.001). Pre-planned subgroup analysis showed statistically significant benefit with cabazitaxel in almost all sub-groups.
- A post-hoc analysis, results of CARD demonstrated that a second ART therapy, (after receiving a first ART treatment of either abi or enza) was minimally efficacious, especially compared to the efficacy of receiving cabazitaxel after first ART therapy.
- These data suggest that mCRPC patients who have received prior docetaxel and either abi or enza should receive cabazitaxel as a third-line therapy, especially if progression with first line abiraterone or prednisone occurs within 12 months of initiation.
- Cabazitaxel represents an approved, and in select provinces, a funded taxane for use in mCRPC in Canada (cabazitaxel is covered by provincial drug programs in AB, SK, MB, ON, QC, NB, NS and NFLD). Cabazitaxel is also approved for use at both 25 mg/m² and 20 mg/m² (recommended) doses (at discretion of treating healthcare provider).

869P - Real-world use of radium-223 for treatment of metastatic castration resistant prostate cancer (mCRPC): Results from the Dutch CAPRI registry

Malou C. Kuppen et al.

Results: 288 patients treated with Ra-223 were included in this analysis. 90% were pretreated with one or more lines of LPD (38% ≥ 1 line). 33% of DOC-naïve patients were treated with Ra-223 as line 1. Baseline characteristics are shown in the table. DOC-naïve patients had prognostic favorable baseline characteristics compared to post-DOC patients, namely higher hemoglobin (7.9 vs 7.4 mmol/L, p < 0.01), lower PSA (85 vs 147 μg/L, p < 0.01) and longer period from castration to mCRPC (16.8 vs 13.1 months, p < 0.01). 47% completed all 6 cycles. 43% were alive or lost-to-follow-up at database cutoff. Median overall survival was 12.2 months (IQR 7-24 months), with longer median overall survival in DOC-naïve compared to post-DOC patients (17.0 vs 11.2 months, p < 0.01).
ART, androgen-receptor targeting drugs (i.e. abiraterone acetate or enzalutamide)

Conclusions: Although Ra-223 was positioned as a later line of mCRPC in this Dutch real-world practice than in the ALSYMPCA trial, overall survival was comparable. This is probably explained by adequate patient selection. Further research on the best timing of Ra-223 in the treatment of mCRPC is awaited.

CARE™ FACULTY SUMMARY AND PERSPECTIVES:

- The alpha emitter known as radium-223 (Ra-223) has demonstrated efficacy in the treatment of castration-resistant prostate cancer in the presence of bone metastasis. For example, results from the ALSYMPCA trial demonstrated an OS benefit for patients treated with Ra-223 (over placebo) in both docetaxel pre-treated and docetaxel naïve mCRPC patients.

- Despite the fact that Ra-223 is efficacious and is among the only clinically used therapeutic radiopharmaceuticals that emits alpha particles, there is a need for data on sequencing and real-word outcomes.

- Analysis of the results of the Dutch CAPRI registry aim to investigate the use of Ra-223 and outcomes in daily practice (data from the Netherlands).

- In CAPRI:
  - 90% of patients were treated with one or more lines of life prolonging agents (LPDs).
  - 120 patients were docetaxel naïve while 168 patients had received prior docetaxel.
  - Median overall survival was 12.2 months, with longer median OS in docetaxel-naïve compared to post-docetaxel patients (17.0 versus 11.2 months, p < 0.01).

- Overall, Ra-223 demonstrated a comparable overall survival in CAPRI and ALSYMPCA despite the fact that Ra-223 was delivered as a later line of mCRPC therapy in CAPRI.

- Results of CAPRI suggest that Canadian prostate cancer treaters can use Ra-223 as a “later” line of therapy without having to compromise the potential OS benefit and while still reaping the benefits of an alpha particle emitter.

- More research, especially real-world data, is needed to optimize the timing of Ra-223 treatment.

Table 2: 869P

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 N = 288</th>
<th>Doc-naive N = 120</th>
<th>Post-doc N = 168</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age ≥75 years (%)</strong></td>
<td>46</td>
<td>63</td>
<td>33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Extent of disease (%) N0 / N1 / Nx M0 / M1 / Mx (visceral)</strong></td>
<td>54 / 20 / 26 71 / 4 / 26</td>
<td>57 / 23 / 21 76 / 3 / 21</td>
<td>52 / 18 / 30 67 / 4 / 29</td>
<td>0.62 0.78</td>
</tr>
<tr>
<td><strong>Charlson score (%) 6 7-8 9-10 &gt;10</strong></td>
<td>64 30 61</td>
<td>64 30 51</td>
<td>63 30 61</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>ECOG (%) 0 1 &gt;1 Missing</strong></td>
<td>19 48 13 20</td>
<td>24 43 13 19</td>
<td>16 51 13 20</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Hb, mmol/L Median (IQR) Missing (%)</strong></td>
<td>7.7 (6.8-8.3) 10</td>
<td>7.9 (7.1-8.4) 10</td>
<td>7.4 (6.6-8.1) 10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>LDH, U/L Median (IQR) Missing (%)</strong></td>
<td>243 (201-310) 33</td>
<td>240 (205-288) 31</td>
<td>248 (197-332) 34</td>
<td>0.60</td>
</tr>
<tr>
<td><strong>ALP, U/L Median (IQR) Missing (%)</strong></td>
<td>153 (91-267) 14</td>
<td>139 (87-227) 14</td>
<td>167 (94-274) 14</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>PSA, μg/L Median (IQR) Missing (%)</strong></td>
<td>124 (48-344) 13</td>
<td>85 (44-205) 14</td>
<td>147 (55-444) 13</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Period from castration to mCRPC, months Median (IQR)</strong></td>
<td>14.3 (8-27)</td>
<td>16.8 (9-28)</td>
<td>13.1 (8-23)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Previous ART use, % Yes No</strong></td>
<td>80 20</td>
<td>76 24</td>
<td>83 17</td>
<td>0.12</td>
</tr>
</tbody>
</table>
LBA50 - Pre-specified interim analysis of GALAHAD: A phase II study of niraparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD)

Matthew R. Smith et al.

Results: As of 23 May 2019, 165 pts were enrolled, of whom 81 had biallelic DRD (46 BRCA and 35 non-BRCA) and had a minimum of 16 weeks of follow up. 51/81 had measurable disease at baseline (29 BRCA and 22 non-BRCA); 47% of pts had visceral metastases. Median follow-up in BRCA and non-BRCA was 7.3 and 6.4 mo, respectively. In BRCA, ORR was 41% and CRR was 63% (Table 3); median duration of objective response was 5.5 mo (range: 3.5–9.2). 7/12 BRCA responses were ongoing. Median rPFS and OS in BRCA were 8.2 and 12.6 mo, respectively. In non-BRCA, objective response was noted in 2/22 pts (both had FANCA) and CRR was 17%; durations of objective response were 3.8 and 6.5 mo, respectively. Grade 3/4 treatment-emergent adverse events were mostly hematologic—anemia (29%), thrombocytopenia (15%) and neutropenia (7%)—and managed with dose interruption or modification.

Table 3: LBA50

<table>
<thead>
<tr>
<th>Response</th>
<th>All biallelic DRD (n = 81)</th>
<th>BRCA1/2 (n = 46)</th>
<th>Non-BRCA (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%) (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Objective RR</td>
<td>12/29 (41) (23.5, 61.1)</td>
<td>2/22 (9) (11, 29.2)</td>
<td></td>
</tr>
<tr>
<td>PSA_{50}</td>
<td>23/46 (50) (34.9, 65.1)</td>
<td>1/35 (3) (0.1, 14.9)</td>
<td></td>
</tr>
<tr>
<td>CTC Conversion</td>
<td>18/38 (47) (31.0, 64.2)</td>
<td>5/24 (21) (7.1, 42.2)</td>
<td></td>
</tr>
<tr>
<td>CRR</td>
<td>29/46 (63) (47.6, 76.8)</td>
<td>6/35 (17) (6.6, 33.7)</td>
<td></td>
</tr>
<tr>
<td>Median rPFS, mo (95% CI)</td>
<td>8.2 (5.2, 11.1)</td>
<td>5.3 (1.9, 5.7)</td>
<td></td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>12.6 (9.2, 15.7)</td>
<td>14.0 (5.3, 20.1)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CRR, composite response rate; CTC, circulating tumor cells; DRD, DNA-repair gene defects; ORR, objective response rate; OS, overall survival; PSA_{50}, ≥50% decline in prostate-specific antigen; rPFS, radiographic progression-free survival.

Conclusions: Niraparib demonstrates clinical activity in pts with treatment-refractory mCRPC with durable responses particularly in biallelic BRCA mutation carriers.

CARE™ FACULTY SUMMARY AND PERSPECTIVES:

• Managing patients with treatment refractory mCRPC (especially after progression on a taxane and androgen receptor-targeted therapy) is an area of important unmet medical need.

• GALAHAD sought to assess niraparib (a highly selective inhibitor of PARP-1 and PARP-2 DNA repair polymerases) as a therapy for patients with mCRPC and DNA-repair gene defects (DRDs) who had progressed on a taxane and androgen receptor therapy).

• DRD status was evaluated by a plasma or tissue-based test and defined as having biallelic alterations in BRCA1/2 (BRCA), ATM, FANCA, PALB2, CHEK2, BRIP1, or HDAC2.

• Results from GALAHAD suggest that patients with BRCA 1 and 2 alterations benefit more from niraparib treatment than patients without BRCA alterations (ORR of 41% versus 9%, CRR of 63% versus 17%).

• Findings from GALAHAD are in-line with the results of the PROfound study and suggest that mCRPC patients with DRDs in BRCA can experience durable responses through PARP inhibition.
844O - Docetaxel for hormone-naïve prostate cancer: Results from long-term follow-up of metastatic (M1) patients in the STAMPEDE randomised trial (NCT00268476) and sub-group analysis by metastatic burden

Nicholas D. James et al.

Results: Median follow-up was ∼6.5yr, compared to ∼3.5yr when last reported. There were 494 deaths on SOC (41% increase in deaths compared to previous report), with median OS = 43.1 months (m). There was good evidence of benefit of SOC+Doc on OS (median = 59.1m, HR = 0.81, 95% CI 0.69-0.95, P = 0.009). Metastatic burden was assessable for 830/1086 (76%) pts; subgroups were representative of the full M1 cohort in terms of stratification factors. There was no evidence of heterogeneity of Doc effect between the LB and HB subgroups (interaction P = 0.827; LB HR = 0.76, 95%CI 0.54-1.07, P = 0.107; HB HR = 0.81, 95%CI 0.64-1.02, P = 0.064). Analysis of other outcomes also found evidence of benefit of SOC+Doc over SOC in failure-free survival (FFS; HR = 0.66, 95% CI 0.57-0.76, P < 0.001) and progression-free survival (PFS; HR = 0.69, 95% CI 0.59-0.81, P < 0.001), and no evidence of heterogeneity of Doc effect between metastatic burden subgroups for either outcome (FFS; P = 0.792; PFS: P = 0.855). There was no evidence that SOC+Doc resulted in late (after 1yr) G3-5 toxicity compared to SOC (27% vs 28% respectively).

Conclusions: The clinically significant benefit in survival for upfront Doc persists after longer follow-up, with no evidence that the benefit differed dependent on disease burden. We advocate that upfront Doc is considered for both LB and HB M1 pts.

CARE™ FACULTY SUMMARY AND PERSPECTIVES:

• The STAMPEDE trial previously demonstrated that metastatic prostate cancer patients with high-volume disease (or high-burden, HB) would experience an OS benefit with docetaxel (DOC), when starting long-term ADT.

• However, questions remained regarding whether patients with metastatic (M1) low burden (LB) PC would also benefit from DOC treatment.

• The sub-group analysis of STAMPEDE suggests that there is no evidence to indicate that the DOC benefits will differ depending on disease burden.

• Docetaxel is an approved taxane for metastatic prostate cancer in Canada and physicians should consider it as a treatment option for M1 PC patients, regardless of disease burden.

853P - ARCHES - The role of androgen deprivation therapy (ADT) with enzalutamide (ENZA) or placebo (PBO) in metastatic hormone-sensitive prostate cancer (mHSPC): Post hoc analyses of high and low disease volume and risk groups

Arnulf Stenzl et al.

Results: 1150 pts were randomized (ENZA + ADT, n = 574; PBO + ADT, n = 576). Median follow-up was 14.4 months. ENZA + ADT significantly improved rPFS (hazard ratio [95% CI] 0.39 [0.30, 0.50]; p < 0.0001). ENZA + ADT pts significantly benefited from prolonged rPFS in all subgroups (Table 4). Significant treatment benefits were observed with ENZA + ADT in several secondary clinical endpoints in the overall population and in both high and low disease volume and risk groups (Table 4). High QoL at baseline was maintained over time. OS data are immature. Adverse events (AEs) were reported in 85.1% of ENZA + ADT vs. 85.9% of PBO + ADT pts, with no unexpected AEs.

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HORMONE SENSITIVE PROSTATE CANCER (HSPC) CONTINUED

<table>
<thead>
<tr>
<th>Overall (n=1150)</th>
<th>Low-volume disease a (n=423)</th>
<th>High-volume disease a (n=727)</th>
<th>Low risk b (n=556)</th>
<th>High risk b (n=511)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>HR (95% CI) c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rPFS d</td>
<td>0.39 (0.30, 0.50)</td>
<td>0.25 (0.14, 0.46)</td>
<td>0.43 (0.33, 0.57)</td>
<td>0.42 (0.28, 0.62)</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>19 48 13 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to PSA progression</td>
<td>0.19 (0.13, 0.26)</td>
<td>0.08 (0.03, 0.20)</td>
<td>0.22 (0.16, 0.32)</td>
<td>0.14 (0.08, 0.25)</td>
</tr>
<tr>
<td>Time to castration resistance</td>
<td>0.28 (0.22, 0.36)</td>
<td>0.18 (0.10, 0.32)</td>
<td>0.32 (0.24, 0.41)</td>
<td>0.27 (0.18, 0.39)</td>
</tr>
<tr>
<td>Time to first SSE</td>
<td>0.52 (0.33, 0.80)</td>
<td>0.25 (0.07, 0.91)</td>
<td>0.59 (0.37, 0.95)</td>
<td>0.39 (0.19, 0.81)</td>
</tr>
<tr>
<td>Time to new antineoplastic therapy</td>
<td>0.28 (0.20, 0.40)</td>
<td>0.39 (0.18, 0.82)</td>
<td>0.27 (0.18, 0.40)</td>
<td>0.28 (0.16, 0.50)</td>
</tr>
<tr>
<td>Rate difference (95% CI) e</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA undetectable (&lt;0.2 ng/mL) rate, f %</td>
<td>50.5 (45.3, 55.7)</td>
<td>48.4 (39.3, 57.4)</td>
<td>50.7 (44.5, 57.0)</td>
<td>54.7 (47.2, 62.1)</td>
</tr>
<tr>
<td>ORR, f %</td>
<td>19.3 (10.4, 28.2)</td>
<td>211 (5.0, 37.3)</td>
<td>18.6 (7.9, 29.3)</td>
<td>16.4 (2.9, 29.9)</td>
</tr>
</tbody>
</table>

a - Defined as per CHAARTED trial criteria; high volume is defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis (Sweeney et al, New Engl J Med 2014);
b - Defined as per LATITUDE trial criteria; high-risk patients had ≥ 2 of the following: Gleason score of ≥ 8 (scale of 2–10), ≥ 3 bone lesions and/or the presence of measurable visceral metastasis (Fizazi et al, New Engl J Med 2017);
c - HR < 1 favors ENZA + ADT; HR > 1 favors PBO + ADT;
d - Assessed by ICR or death within 24 weeks of treatment discontinuation;
e - Difference > 0 favors ENZA + ADT; difference < 0 favors PBO + ADT;
f - Difference > 0 favors ENZA + ADT; difference < 0 favors PBO + ADT;
f - Of those with detectable PSA or measurable disease at baseline, respectively. ADT=androgen deprivation therapy; CI=confidence interval; ENZA=enzalutamide; HR=hazard ratio; ICR=independent central review; PBO=placebo; PSA=prostate-specific antigen; ORR=objective response rate; OS=overall survival; QoL=quality of life; rPFS=radio graphic progression free survival; SSE=symptomatic skeletal event.

Conclusions: ENZA + ADT treatment showed efficacy benefit across all mHSPC pts, irrespective of disease volume and risk group. Similar delays in rPFS, symptomatic skeletal events, PSA progression, castration resistance, and improvements in radiographic responses and PSA declines, with maintenance of high QoL over time, were observed. Preliminary safety analysis appears consistent with the safety profile of ENZA in previous CRPC clinical trials.

CARE™ FACULTY SUMMARY AND PERSPECTIVES:

• The efficacy of enzalutamide (enza) has been demonstrated in patients with CRPC in previous studies. This post-hoc analysis of ARCHES aims to investigate the role of enza + ADT in patients with mHSPC at different disease volumes and risks.

• In the ARCHES post-hoc analysis:
  • Primary endpoint was radiographic progression-free survival (rPFS).
  • Secondary endpoints included prostate-specific antigen (PSA) progression and radiographic responses, overall survival (OS), and quality of life (QoL).

• Enza + ADT demonstrated efficacy across all mHSPC patients, however it is not (at the time of publication) approved for hormone sensitive PC in Canada.

• Patients and physicians would benefit from the approved use of enzalutamide for mHSPC. Data suggests enza + ADT provides positive outcomes in this setting independent of disease volume and risk without the development of new safety signals.
883P - Androgen receptor (AR) aberrations in patients (Pts) with metastatic castration-sensitive prostate cancer (mCSPC) treated with apalutamide (APA) plus androgen deprivation therapy (ADT) in TITAN

Kim N. Chi et al.

Results: BL characteristics of pts were balanced between biomarker-positive groups. Among aberrations at BL, AR amplification was associated with longer duration of prior ADT (4.2 mo vs 1.6 mo, pts with vs without AR amplification; p = 0.034). ctDNA % and frequency of AR aberrations increased from BL to EOT. At EOT, ctDNA % was similar in APA and PBO groups (60% and 66%), and AR aberrations were less frequent with APA vs PBO (Table 5). Regardless of treatment group, OS was significantly shorter with detection of any AR aberration at EOT (OS: 2.7 [1.1-6.6], p = 0.0278, APA; 6.1 [1.9-20.3], p = 0.0007, PBO). Detection of any AR aberration at EOT was significantly associated with duration on first subsequent therapy (2.0 [1.0-4.0], p = 0.0386).

Conclusions: In TITAN, AR amplification at BL was associated with even brief ADT exposure. AR aberrations were fewer at EOT with APA vs PBO. Pts with AR aberrations at EOT had worse outcomes vs pts without. Taken together, these findings suggest that early APA + ADT provides long-term benefits vs ADT alone without increased acquisition of AR aberrations. The detailed biological mechanisms underlying these findings need to be further studied.

<table>
<thead>
<tr>
<th>Table 5: 883P Frequency of AR aberrations at BL and EOT</th>
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<tbody>
<tr>
<td>n, (n/N%)</td>
</tr>
<tr>
<td>ARv7</td>
</tr>
<tr>
<td>AR mutation</td>
</tr>
<tr>
<td>AR amplification</td>
</tr>
<tr>
<td>Any AR aberrationa</td>
</tr>
</tbody>
</table>

a - Only pts with ARv7, AR amplification, and AR mutation measured are reported.

b - From Fisher’s exact test for comparison vs PBO, p = 0.04.

Conclusions: In TITAN, AR amplification at BL was associated with even brief ADT exposure. AR aberrations were fewer at EOT with APA vs PBO. Pts with AR aberrations at EOT had worse outcomes vs pts without. Taken together, these findings suggest that early APA + ADT provides long-term benefits vs ADT alone without increased acquisition of AR aberrations. The detailed biological mechanisms underlying these findings need to be further studied.

CARE™ FACULTY SUMMARY AND PERSPECTIVES:

- Androgen receptor (AR) aberrations in patients with prostate cancer can be associated with treatment resistance and poor patient outcomes.
- In the TITAN trial, apalutamide (a non-steroidal androgen receptor inhibitor) + ADT improved OS versus placebo + ADT in patients with mCSPC. The study presented in ESMO 2019 abstract 883P aims to investigate the AR aberrations at baseline (BL) and end of treatment (EOT) from the TITAN study outcomes.
- Results of ESMO 2019 abstract 883P suggest:
  - Any AR aberrations at EOT were associated with poorer treatment outcomes (including shorter OS).
  - Apalutamide + ADT was not associated with increased acquisition of AR aberrations.
- Although understanding of the underlying biology behind AR aberrations and their causes could improve with further study, this analysis of the TITAN outcomes suggests that treating mCSPC patients with apalutamide + ADT provides benefits without increased risk of developing AR aberrations.
- At the time of publication, apalutamide has been approved for use in mCSPC patients by the FDA (based on TITAN results), however it is not approved for patients with mCSPC by Health Canada.
- Canadians with prostate cancer would likely benefit from the use of apalutamide in the mCSPC setting as it is associated with OS benefit and not associated with increased AR aberrations.
RESULTS:
Concomitant rifampicin led to a 3.5-fold decrease in DARO area under the curve (AUC) vs DARO alone. ICZ resulted in 1.8-fold increase in DARO AUC vs DARO alone. No significant effect of comedications that are CYP or P-gp inhibitors was identified in the popPK analysis; proton pump inhibitors did not significantly affect the PK of DARO. Effects of DARO on CYP inhibition in vitro were negligible and coadministration of midazolam or dabigatran showed no clinically relevant effects. Rosuvastatin AUC increased by 5.2-fold with DARO vs rosuvastatin alone, attributed mainly to BCRP inhibition. The incidence of AEs in ARAMIS was low; comedication use (98.7% in DARO, 98.0% in PBO arms) and AE profile were similar between study arms.

CONCLUSIONS:
DDIs with DARO and P-gp or CYP enzyme substrates, e.g. antithrombotics, calcium channel blockers or proton pump inhibitors, are not expected. Strong CYP3A4 inducers, e.g. rifampicin and carbamazepine, showed some interaction with DARO. Effects of CYP3A4 or P-gp inhibitors on DARO were not considered clinically relevant. DARO may increase the exposure of concomitant BCRP substrates, e.g. statins, although a safety and AE analysis from ARAMIS did not indicate any relevant impact of DARO.

**CARE™ SPOTLIGHT ON: A NOVEL ANDROGEN RECEPTOR INHIBITOR FOR nmCRPC AND mCSPC**

This CARE™ Spotlight highlights apalutamide, a novel androgen receptor inhibitor which received a Health Canada approval in 2018 and saw additional data releases at ESMO 2019.

Multidisciplinary CARE™ Faculty perspectives consider:

- OS in nmCRPC with an update from SPARTAN second interim analysis (IA2)
- HRQOL from TITAN Phase 3, patient reported outcomes (PROs)

**ESMO 2019 ABSTRACT 8430 - SPARTAN IA2**

Apalutamide (APA) and overall survival (OS) in patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC): updated results from the phase III SPARTAN study

Eric. J. Small et al.


**Background:** In the SPARTAN study, compared with placebo + ADT, apalutamide added to ongoing androgen deprivation therapy significantly prolonged metastasis-free survival (MFS) and time to symptomatic progression in patients with high-risk nonmetastatic castration-resistant prostate cancer (nmCRPC). Overall survival (OS) results at the first interim analysis (IA1) were immature, with 104 of 427 (24%) events required for planned final OS analysis (IA1 median follow-up time was 20.3 months). Here, we report the results of a second prespecified interim analysis (IA2).

**Methods:** One thousand two hundred and seven patients with nmCRPC were randomized 2 : 1 to apalutamide (240mg daily) + ADT or placebo + ADT. The primary end point of the study was MFS. Subsequent therapy for metastatic CRPC was permitted. When the primary end point was met, the study was unblinded. Patients (n=76, approximately 19%) receiving placebo who had not yet developed metastases were offered open-label apalutamide. At IA2, pre-specified analysis of OS was undertaken, using a group-sequential testing procedure with O’Brien-Fleming-type alpha spending function. Safety and second progression-free survival (PFS2) were assessed, as was time to chemotherapy.

**Results:** Median follow-up was 41 months. With 285 (67% of required) OS events, apalutamide was associated with an improved OS compared with placebo (HR 0.75; 95% CI 0.59–0.96; P=0.0197), although the P-value did not cross the prespecified O’Brien-Fleming boundary of 0.0121. Apalutamide improved PFS2 (HR 0.55; 95% CI 0.45–0.68; p <0.0001). At IA2, 69% of placebo-treated and 40% of apalutamide-treated patients had received subsequent life-prolonging therapy for metastatic CRPC. No new safety signals were observed. **continued on next page...**
Conclusions: In patients with nmCRPC, apalutamide was associated with a 25% reduction in risk of death compared with placebo. This OS benefit was observed despite crossover of placebo-treated patients and higher rates of subsequent life-prolonging therapy for the placebo group.

CARE™ FACULTY PERSPECTIVES: ESMO 2019 ABSTRACT 8430 - SPARTAN IA2

Dr. Sebastien Hotte (McMaster University)
Medical Oncology - CARE™ Faculty Perspectives:

As one of the novel androgen receptor antagonist therapies (ARATs), apalutamide has previously demonstrated a clear clinical benefit in preventing or delaying the appearance of overt metastatic disease. This was similarly observed in studies of other ARATs studied in this population, specifically enzalutamide and darolutamide. Although it has been acknowledged that an overall survival (OS) benefit may be difficult to achieve given the long survival and successful subsequent therapies of patients with M0 CRPC, this analysis, even if not technically positive given the prespecified P-value boundary, suggests that apalutamide may provide clinically relevant OS improvements in these patients. It is important to realize that the patients randomized to SPARTAN had a doubling time of only four months and therefore represented a group of patients with fairly aggressive disease – it is plausible that an OS improvement may not be observed in patients with less aggressive (doubling time 6 to 10 months) disease.

Dr. Anil Kapoor (McMaster University)
Urology - CARE™ Faculty Perspectives:

When managing prostate cancer patients in the nonmetastatic setting, the ability to delay metastasis, and therefore disease progression, is a desirable therapeutic quality - one which was observed in the results of the SPARTAN trial investigating apalutamide (MFS was 40.5 months in the apalutamide group versus 16.2 months in the placebo group). Now a second interim analysis of the SPARTAN trial results suggest that the MFS benefit of apalutamide is sustained through a median follow-up of 41 months leading to an OS benefit and 25% reduction in the risk of death. Apalutamide is a Health Canada approved androgen receptor antagonist for nmCRPC and Canadian urologists should consider the potential benefits of its use in the nonmetastatic setting.

Dr. Brita Danielson (University of Alberta)
Radiation Oncology - CARE™ Faculty Perspectives:

This study further demonstrates the benefit of using apalutamide for patients with high risk nmCRPC. The initial interim analysis of SPARTAN showed a significant improvement of metastases-free survival (MFS), and there was speculation whether this would translate into an overall survival (OS) benefit. With a median follow-up of just over 3 years, there is now a strong suggestion that OS is also improved in this patient population. In addition, it was encouraging that no new toxicities were noted. Overall, this second analysis of the SPARTAN trial reinforces the effectiveness and tolerability of apalutamide for high-risk nmCRPC patients.
Patient-reported outcomes (PROs) from TITAN: A phase III, randomized, double-blind study of apalutamide (APA) versus placebo (PBO) added to androgen deprivation therapy (ADT) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC)

Neeraj Agarwal et al.

Link to publication: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30620-5/fulltext#seccestitle10

Background: In the phase 3 TITAN study, the addition of apalutamide to androgen deprivation therapy (ADT) significantly improved the primary endpoints of overall survival and radiographic progression-free survival in patients with metastatic castration-sensitive prostate cancer. We aimed to assess health-related quality of life (HRQOL) in TITAN, including pain and fatigue.

Methods: In this randomised, placebo-controlled, double-blind, phase 3 study, patients with metastatic castration-sensitive prostate cancer (defined as not receiving ADT at the time of metastatic disease progression) aged 18 years and older, receiving continuous ADT (selected at the investigator’s discretion), and with an Eastern Cooperative Oncology Group performance status score of 0 or 1 were randomly assigned (1:1), using an interactive web response system, to receive oral apalutamide (four 60 mg tablets, once daily) or matching placebo. Previous localised disease treatment or previous docetaxel for metastatic castration-sensitive prostate cancer were allowed. Randomisation was stratified by Gleason score at diagnosis, region, and previous docetaxel treatment. Randomisation was done using randomly permuted blocks (block size of four). Investigators, research staff, sponsor study team, and patients were masked to the identities of test and control treatments. Patient-reported outcomes were prespecified exploratory endpoints and were the Brief Pain Inventory- Short Form (BPI-SF), Brief Fatigue Inventory (BFI), Functional Assessment of Cancer Therapy-Prostate (FACT-P), and EuroQoL 5D questionnaire 5 level (EQ-5D-5L). BPI and BFI were completed for 7 consecutive days (days –6 to 1 inclusive of each cycle visit), then at months 4, 8, and 12 in follow-up. FACT-P and EQ-5D-5L were completed during cycles 1–7, then every other cycle until the end of treatment, and at months 4, 8, and 12 in follow-up. Analyses were based on the intention-to-treat population. Missing patient-reported outcome assessments were calculated as the expected number of assessments for a visit minus the actual number of assessments received for that visit. For time-to-event endpoints, when median values could not be calculated because less than 50% of patients had degradation, 25th percentiles were compared. This study is registered with ClinicalTrials.gov, number NCT02489318, and is ongoing.

Results: Between Dec 9, 2015, and July 25, 2017, 1052 eligible patients were enrolled randomly assigned to apalutamide (n=525) or placebo (n=527). Data cutoff for this analysis of patient-reported outcomes was Nov 23, 2018. Median follow-up for time to pain-related endpoints ranged from 19.4 to 22.1 months. Patients were mostly asymptomatic at baseline: on the BPI-SF pain severity scale of 0–10, median pain scores (indicating worst pain in the past 24 h) were 1.14 (IQR 0–3.17) in the apalutamide group and 1.00 (0–2.86) in the placebo group, and median worst fatigue scores on the BFI were 1.29 (IQR 0–3.29) in the apalutamide group and 1.43 (0.14–3.14) in the placebo group. Patient experience of pain and fatigue (intensity and interference) did not differ between the groups for the duration of treatment. Median time to worst pain intensity progression was 19.09 months (95% CI 11.04–not reached) in the apalutamide group versus 11.99 months (8.28–18.46) in the placebo group (HR 0.89 [95% CI 0.75–1.06]; p=0.20). Median time to pain interference progression was not reached in either group (95% CI 28.58–not reached in the apalutamide group; not reached–not reached in the placebo group). 25th percentiles for time to pain interference progression were 9.17 months (5.55–11.96) in the apalutamide group and 6.24 months (4.63–7.43) in the placebo group (HR 0.90 [95% CI 0.73–1.10]; p=0.29). FACT-P total scores and EQ-5D-5L data showed preservation of HRQOL in both groups. The median time to deterioration as determined by FACT-P total score was 8.87 months (95% CI 4.70–11.10) in the apalutamide group and 9.23 months (7.39–12.91) in the placebo group (HR 1.02 [95% CI 0.85–1.22]; p=0.85).

Conclusions: Apalutamide with ADT is a well-tolerated and effective option for men with metastatic castration sensitive prostate cancer. The combination significantly improves survival outcomes compared with ADT alone while maintaining HRQOL despite additive androgen blockade.
TITAN evaluated ADT plus either the ARAT apalutamide or placebo and found a clinically relevant and statistically significant improvement in OS in men who present with metastatic disease. Along with docetaxel and abiraterone (as well as enzalutamide given the recently presented ENZAMET study), apalutamide is now another option for patients with mCSPC. The trials evaluating docetaxel (CHAARTED) and abiraterone (LATITUDE) both presented and published their impact on HRQOL and PROs. Apalutamide’s possible side effects include rash and fatigue and there was some concern these may impact negatively on patient reported outcomes. However, the TITAN analysis of HRQOL suggests that quality of life is preserved in a population of men who were largely asymptomatic at the time of study entry and, when clinically available and reimbursed in Canada, apalutamide can be safely recommended as one of the options for men with mCSPC.

In addition to clinical, quantitative measures, patient comfort with a certain therapy and the way in which it makes patients “feel” can be important considerations for making treatment decisions. The fact that apalutamide was able to display OS and rPFS benefits without compromising HRQOL indicates that it is both efficacious and tolerable. Because patients do not experience spikes in pain or fatigue when on apalutamide, they may be more inclined to have strong treatment compliance, thereby improving efficacy. Apalutamide is not currently approved for mCSPC in Canada, however it may represent a therapy that is effective from both a clinical and PRO perspective.

Androgen deprivation therapy (ADT) has long been the backbone of treatment in advanced prostate cancer, and comes with its own toxicities, including fatigue, hot flashes and sweats, sexual dysfunction, decreased muscle mass, and decreased bone density. Patients may also experience pain from bone metastases. The initial report from the TITAN study demonstrated that the addition of the novel oral androgen receptor targeted agent apalutamide improved overall survival (OS) in patients with metastatic castration-sensitive prostate cancer (mCSPC), but its effect on patients’ pain scores and health-related quality of life (HRQOL) was not known. With the results of this report, we can now be reassured that there is no worsening of HRQOL of pain for patients on apalutamide compared to those on placebo for the duration of treatment. This provides further support for the early treatment of patients with mCSPC, even in the absence of symptoms.
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