INTRODUCTION

The annual ESMO 2021 Congress provides updates on scientific developments in Oncology. CARE™ Prostate Cancer Faculty reviewed congress materials and have identified the most relevant clinical trial updates from a Canadian perspective.

Faculty Involved in this Review:

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This report will cover:

Longer-term efficacy data/additional follow-up from:

- Abiraterone acetate plus prednisolone (AAP) with or without enzalutamide (ENZ) added to androgen deprivation therapy (ADT) compared to ADT alone for men with high-risk non-metastatic (M0) prostate cancer (PCa): Combined analysis from two comparisons in the STAMPEDE platform protocol
- Final overall survival (OS) analysis from ARCHES: A phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) + androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC)
- Apalutamide (APA) for advanced prostate cancer in older patients (pts): Combined analysis of TITAN & SPARTAN
- Pembrolizumab (pembro) monotherapy for docetaxel-pretreated metastatic castration-resistant prostate cancer (mCRPC): Updated analyses with 4 years of follow-up from cohorts 1-3 of the KEYNOTE-199 study

New data on AEs and QoL considerations:

- Time course profile of adverse events of interest and serious adverse events with darolutamide in the ARAMIS trial
- Objective computerized cognitive assessment in men with metastatic castrate-resistant prostate cancer (mCRPC) randomly receiving darolutamide or enzalutamide in the ODENZA trial
- Health-related quality of life (HRQoL), pain and safety outcomes in the phase III VISION study of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer
- Pain efficacy with radium-223 (Ra-223) in the REASSURE global, prospective, observational study of men with metastatic castration-resistant prostate cancer (mCRPC) and in the PARABO observational study

Novel strategies and agents in development:

- A phase III trial with a 2x2 factorial design in men with de novo metastatic castration-sensitive prostate cancer: Overall survival with abiraterone acetate plus prednisone in PEACE-I
- CheckMate 9KD cohort A2 final analysis: Nivolumab (NIVO) + rucaparib for chemotherapy (CT)-naive metastatic castration-resistant prostate cancer (mCRPC)

To access the full abstract content and meeting resources please visit: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021?hit=ohp
KEY NEWS FROM ESMO 2021
What follows is a review of select clinical research from the ESMO 2021 Congress.

Longer-term Data and Additional Follow-up

LBA4_PR. Abiraterone acetate plus prednisolone (AAP) with or without enzalutamide (ENZ) added to androgen deprivation therapy (ADT) compared to ADT alone for men with high-risk non-metastatic (M0) prostate cancer (PCa): Combined analysis from two comparisons in the STAMPEDE platform protocol. Gerhardt Attard et al.

Trial Highlights
1974 M0 pts at 113 sites in UK and Switzerland were randomized
Median months to stopping AAP, 23.7 (IQR: 17.6-24.1); AAP when given with ENZ, 20.7 (IQR: 4.4-24); ENZ, 23.2 (IQR: 6.3-24).
2 y of AAP-based therapy significantly improves MFS & survival of high-risk M0 PCa starting ADT
• AAP-based therapy improved MFS (HR 0.53, 95% CI 0.44-0.64, P=2.9×10-11) & survival (HR 0.60, 95% CI 0.48-0.73, P=9.3×10-7); 6-y MFS from 69% to 82%, 6-y survival from 77% to 86%.

Treatment effect was consistent in major subgroups and between AAP & AAP + ENZ randomisation periods (MFS HR=0.54, 95% CI 0.43-0.68; HR=0.53, 95% CI 0.39-0.71 respectively; interaction HR = 1.02, 95% CI: 0.70-1.50, p=0.908)

CARE™ Canadian Perspective
This arm of the ongoing STAMPEDE trial has shown not only a MFS benefit but a very significant OS benefit to 2 years of adjuvant abiraterone/prednisone (+/- enzalutamide) in addition to external beam radiotherapy (EBRT) and ADT for men with localized high risk prostate cancer. The addition of enzalutamide to abiraterone increased toxicity without improving survival outcomes.

This approach may become a new standard of care; however, we await the publication of the trial for further details. Prior to mainstream use, abiraterone will need to be Health Canada approved for this new indication, as well as funded by provincial cancer bodies. Two years of adjuvant abiraterone for high-risk patients will significantly increase patient volumes for prescribers of ARATs, and new models of care may be considered for this patient population (for example, nurse practitioner clinics, or prescribing by the treating radiation oncologist). This study reflects the ongoing evolution of systemic therapies earlier in the disease trajectory of prostate cancer.

LBA25. Final overall survival (OS) analysis from ARCHES: A phase III, randomized, double-blind, placebo (PBO)-controlled study of enzalutamide (ENZA) + androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC).

Andrew Armstrong et al.

Trial Highlights
In ARCHES (NCT02677896), ENZA + ADT reduced risk of radiographic progression and improved secondary outcomes in men with mHSPC over PBO + ADT.
Median treatment duration was 40.2 months on ENZA + ADT, 13.8 months on PBO + ADT, and 23.9 months for crossover patients.
This final analysis demonstrates that ENZA + ADT significantly prolongs survival in men with mHSPC (HR 0.66; 95% confidence interval 0.53, 0.81; p<0.0001) (Figure 1)
The safety profile of ENZA + ADT vs PBO + ADT was consistent with findings from the primary analysis.

CARE™ Canadian Perspective
With ongoing follow-up, the ARCHES trial continues to demonstrate that enzalutamide in addition to ADT provides a significant improvement in overall survival, with a median treatment duration of over 3 years.
Importantly, the safety profile remains acceptable, which is critical when patients are on treatment for this duration. Enzalutamide in addition to ADT is an effective treatment option for all-comers with mCSPC, regardless of disease volume or risk classification.

Figure 1. Median treatment duration: LBA25
**618P. Apalutamide (APA) for advanced prostate cancer in older patients (pts): Combined analysis of TITAN & SPARTAN.**

John Shen et al.

**Trial Highlights**

In TITAN and SPARTAN, APA added to continuous androgen deprivation therapy (ADT) improved prostate-specific antigen (PSA) response, radiographic progression-free survival (rPFS), metastasis-free survival (MFS), and overall survival (OS) in pts with metastatic castration-sensitive prostate cancer (mCSPC) and nonmetastatic castration-resistant prostate cancer (nmCRPC).

1052 mCSPC (525 APA, 527 PBO), and 1207 nmCRPC (806 APA, 401 PBO) pts were assessed.

APA added to ADT improved: PSA50 in all age groups, primary end points in all age groups but ≥80 y TITAN pts, and OS in < 65 and 65-79 y groups in TITAN and < 65 y group in SPARTAN.

HRQoL was maintained regardless of age or treatment group, with low side effect burden.

**CARE™ Canadian Perspective**

Patients with mCSPC and nmCRPC derived clinical benefit and maintained HRQoL from APA plus ADT, but oldest patients had a trend toward less benefit with increasing age, increased AE rates, and shorter treatment duration.

The most important takeaway from results was that there was an increase in many AEs as men got older (incl. falls, skin rash, cardio issues, etc.). When starting men on these agents, a risk-benefit analysis needs to take place and we must acknowledge that some AEs will be worse with older patients.

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**611P - Pembrolizumab (pembro) monotherapy for docetaxel-pretreated metastatic castration-resistant prostate cancer (mCRPC): Updated analyses with 4 years of follow-up from cohorts 1-3 of the KEYNOTE-199 study.**

Emmanuel Antonarakis et al.

**Trial Highlights**

Previous analysis of 3 cohorts of patients (C1: RECIST-measurable, PD-L1+, C2: RECIST-measurable, PD-L1−; C3: bone-predominant irrespective of PD-L1) who were previously treated with a next-generation hormonal agent (NHA) and docetaxel showed durable antitumor activity and a manageable safety profile with pembro.

In patients with measurable disease, ORR was 6.0% (95% CI, 2.6-11.5; 4 CR, 4 PR) in C1 and 3.0% (95% CI, 0.4-10.4; 2 PR) in C2.

Median DOR was not reached in C1 or C2, but 3 pts in C1 continued in response for ≥36 months.

Of all patients, treatment-related AEs occurred in 61.2% (158/258), and grade 3-5 treatment-related AEs occurred in 15.9% (41/258).

- One patient in each cohort died of a treatment-related AE (C1: sepsis; C2: unknown; C3: immune-related pneumonitis).

**CARE™ Canadian Perspective**

After 4 years’ follow-up, pembro monotherapy still showed modest antitumor activity and a manageable safety profile in patients with docetaxel-pretreated mCRPC.

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**WE MUST ACKNOWLEDGE THAT SOME AEs WILL BE WORSE WITH OLDER PATIENTS**

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New Data on AEs and QoL Considerations

630P. Time course profile of adverse events of interest and serious adverse events with darolutamide in the ARAMIS trial.
Christian Gratzke et al.

**Trial Highlights**

Men with nonmetastatic castration-resistant prostate cancer (nmCRPC) are generally asymptomatic and may receive prolonged treatment with androgen receptor inhibitors (ARIs).

During the first 24 months of the DB period, the incidence of AEs of interest in the DARO group was low and ≤2% different from that in the PBO group, except for fatigue:

- In men who had fatigue during the first 24 months (DARO, 12.6% and PBO, 8.3%), almost half of the men experienced fatigue onset during the first month in both arms (DARO, 5.9% vs PBO, 4.0%).

During the first month of DARO and PBO treatment, new event rates were very low and similar for falls (0.2%, 0.7%), fractures (0.4%, 0.5%), mental impairment (0%, 0.4%), hypertension (1.7%, 1.1%), and rash (0.7%, 0.2%).

- The cumulative incidence of rash was 2.9% (PBO 1.1%) at 24 months, with half of the events occurring in the first 4 months and almost all being grade 1 or 2.

The rate of initial onset and cumulative incidence of grade 3/4 AEs and serious AEs were similar for DARO and PBO groups over 24 months.

603P. Objective computerized cognitive assessment in men with metastatic castrate-resistant prostate cancer (mCRPC) randomly receiving darolutamide or enzalutamide in the ODEENZA trial.
Emeline Colomba et al.

**Trial Highlights**

Daro does not significantly penetrate the blood-brain barrier, which may reduce cognitive impairment.

Performance on verbal learning (ISL) was significantly better with Daro at each of the post-baseline assessments, within both periods and when averaged over periods.

Performance on verbal memory (ISRL) was significantly better with Daro at the second period and when averaged over periods, although the effect sizes were less meaningful (second period: -0.4, p=0.01 and overall: -0.29, p=0.0075).

The composite scores reported a moderate benefit in episodic memory after treatment with Daro compared to Enza.

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**CARE™ Canadian Perspective (630P & 603P)**

The time course profile of most AEs of interest, grade 3/4 AEs, and serious AEs confirms the safety profile of DARO, showing a similar onset and cumulative incidence versus PBO. Most events of fatigue were reported early in treatment, and the incidence of rash was very low, with almost all being grade 1 or 2 events. This further supports darolutamide as a very safe therapy that also improves survival outcomes.

In early mCRPC (603P), darolutamide was associated with a statistically significant benefit in verbal learning and verbal memory compared to Enza. Currently daro is not indicated for mCRPC in Canada so this is an interesting cohort for us to look at in parallel with the original study. While many do not have a lot of experience using this agent in this setting, we can be reassured that it was very well tolerated. Limitations with this study included quite small patient numbers and short duration of follow-up.

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**THIS FURTHER SUPPORTS DAROLUTAMIDE AS A VERY SAFE THERAPY THAT ALSO IMPROVES SURVIVAL OUTCOMES**
576MO. Health-related quality of life (HRQoL), pain and safety outcomes in the phase III VISION study of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer.
Karim Fizazi et al.

**Trial Highlights**

\(^{177}\)Lu-PSMA-617) delivers β-particle radiation to prostate-specific membrane antigen (PSMA) expressing cells and the surrounding microenvironment.

HRQoL and pain time-to-worsening analyses favoured the \(^{177}\)Lu-PSMA-617 arm, despite a higher incidence of grade ≥ 3 adverse events versus SOC alone.

No new or unexpected safety concerns were noted, including changes in creatinine clearance.

**CARE™ Canadian Perspective**

\(^{177}\)Lu-PSMA-617 plus SOC was generally well tolerated and delayed time to HRQoL and pain worsening versus SOC alone in patients with advanced mCRPC.

Arguably one of the most dramatic results was the time to worsening pain analyses which favoured the \(^{177}\)Lu-PSMA-617 arm by almost a 12-month difference. This agent appears to be an exciting option for patients in 3rd line or greater that will hopefully be available at our treatment centres soon.

594P. Pain efficacy with radium-223 (Ra-223) in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) in the PARABO observational study
Holger Palmedo et al.

**Trial Highlights**

Of 216 pts with baseline worst pain >1, 128 (59%) had a clinically meaningful pain response; the rate was 60% in pts with ≤20 lesions vs 59% in pts with >20 lesions; 65% in pts with opioid use vs 54% in pts without opioid use; and 67% in pts with 5–6 Ra-223 injections vs 43% in pts with ≤4 injections.

Mean BPI-SF component scores during Ra-223 treatment improved or were maintained from baseline, regardless of EOD or opioid use.

**CARE™ Canadian Perspective**

In real-world settings, patients with BL pain treated with Ra-223 experienced incremental reduction in pain with each cycle, regardless of baseline EOD or concomitant opioid/EBRT use. Benefits were sustained following completion of Ra-223 and complement clinical trial evidence of improved pain-related QoL.

593P - Pain efficacy with radium-223 (Ra-223) in the REASSURE global, prospective, observational study of men with metastatic castration-resistant prostate cancer (mCRPC).
Celestia Higano et al.

**Trial Highlights**

Of 1465 pts who received Ra-223, 1027 (70%) had BL worst pain ≥2; 394/1027 (38%) received no concomitant opioid or EBRT to bone.

During Ra-223 treatment, 566/1027 pts (55%) overall and 228/394 pts (58%) with no concomitant opioid/EBRT achieved a pain response.

Pain severity (BPI-SF score) and interference summary scores (mean of the scores for how pain interfered with 7 daily activities) decreased with each Ra-223 cycle and remained below BL during follow-up.

- By the last follow up, 18% of pts overall and 23% with no concomitant opioid/EBRT reported complete pain relief.

Median OS was 14.7 months (95% confidence interval 13.4, 15.9) overall and 17.6 months (16.5, 19.3) in pts with no concomitant opioid/EBRT.

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**BENEFITS WERE SUSTAINED FOLLOWING COMPLETION OF RA-223 AND COMPLEMENT CLINICAL TRIAL EVIDENCE OF IMPROVED PAIN-RELATED QoL.**

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Trial Highlights

PEACE-1 is a phase 3 trial with a 2x2 factorial design of abiraterone acetate plus prednisone (abiraterone) and/or local radiotherapy.

The median follow-up is 4.4 yrs (n=273 death events in the ADT+docetaxel population).

OS was improved by abiraterone both in the overall population (HR: 0.83, 95% CI: 0.69-0.99, p=0.034; medians: 5.7 vs 4.7 yrs) and in the ADT+docetaxel population (HR: 0.75, 95% CI: 0.59-0.96, p=0.021; medians: NR vs 4.4 yrs).

Among the ADT+docetaxel pts who developed CRPC, 231/263 (88%) then received at least one life-prolonging therapy and 222/263 (84%) at least one ASI in the control arm, compared to 110/141 (78%) and 67/141 (48%) in the abiraterone arm, respectively.

Grade 3-5 adverse events reported in >5% of pts in the ADT+docetaxel population included neutropenic fever (5% vs 5%), neutropenia (10% vs 9%), liver toxicity (6% vs 1%) and hypertension (21% vs 13%) in the abiraterone and control arms, respectively.

CARE™ Canadian Perspective

Adding abiraterone to ADT plus docetaxel improves both rPFS and OS in mCSPC men, even when 84% of men from the control arm subsequently receive an ASI for mCRPC.

The main question resulting from this trial identifying which patients will benefit from triplet therapy (ADT + docetaxel + abiraterone), vs. receiving ADT + docetaxel or ADT + ASI alone. In the current treatment landscape where most patients with mCSPC are patients being treated with an ASI up front, the clinical question of adding abiraterone to docetaxel is simply not as relevant as when this trial was designed. Also, eager awaited are the results from the local radiotherapy (RT) arms, to determine if RT to the prostate provide a benefit in addition to intensification of systemic therapy.

579MO. CheckMate 9KD cohort A2 final analysis: Nivolumab (NIVO) + rucaparib for chemotherapy (CT)-naive metastatic castration-resistant prostate cancer (mCRPC).

Daniel Petrylak et al.

Trial Highlights

Median treatment duration was 4.6 mo for NIVO and 5.5 mo for rucaparib; median follow-up was 17.5 mo.

See Table 1. for efficacy results

CARE™ Canadian Perspective

NIVO + rucaparib is active in pts with HRD+ CT-naive mCRPC.

Longer follow-up is needed to better characterize clinical benefits of adding NIVO to rucaparib for this population.

Table 1. Efficacy Results 579MO

<table>
<thead>
<tr>
<th>NI Outcome (95% CI)</th>
<th>Total (N = 71)</th>
<th>HRD−/not evaluable (N = 37)</th>
<th>HRD+ (N = 34)</th>
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<tbody>
<tr>
<td>Confirmed ORR, %</td>
<td>n = 39 15.4 (5.9–30.5)</td>
<td>n = 19 5.3 (0.1–26.0)</td>
<td>n = 20 25.0 (8.7–49.1)</td>
</tr>
<tr>
<td>Confirmed PSA-RR, %</td>
<td>n = 66 73 (170–39.6)</td>
<td>n = 35 14.3 (4.8–30.3)</td>
<td>n = 31 41.9 (24.5–60.9)</td>
</tr>
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<td>Median rPFS, mo</td>
<td>81 (5.6–10.9)</td>
<td>5.6 (3.7–9.1)</td>
<td>10.9 (6.7–12.0)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>20.2 (14.1–22.8)</td>
<td>19.0 (8.2–22.1)</td>
<td>22.7 (14.1–NE)</td>
</tr>
</tbody>
</table>

*aPts with measurable disease at baseline; ^50% PSA reduction from baseline. NE, not estimable.

IN THE CURRENT TREATMENT LANDSCAPE WHERE MOST PATIENTS WITH MCSPC ARE PATIENTS BEING TREATED WITH AN ASI UP FRONT, THE CLINICAL QUESTION OF ADDING ABIRATERONE TO DOCETAXEL IS SIMPLY NOT AS RELEVANT.
KEY HIGHLIGHTS AND PARTING COMMENTS

Longer-term efficacy data/additional follow-up:
Positive long-term follow up with approaches in high-risk non-metastatic prostate cancer reflect the ongoing evolution of systemic therapies earlier in the disease trajectory of prostate cancer.
- Approval and access to these strategies in Canada is awaited.

Data for APA + ADT in advanced prostate cancer in older patients demonstrate that some AEs (incl. falls, skin rash, cardio issues) can be worse in older patients.
- When starting men on these agents, a risk-benefit analysis needs to take place.

New data on AEs and QoL considerations:
Additional follow-up from the ARAMIS and ODENZA trials support darolutamide as a very safe option for patients that also improves survival outcomes.

177Lu-PSMA-617 will be an exciting option for patients in 3rd line or greater when it is available in our treatment centres.

In real-world settings, benefits in pain efficacy with Ra-223 were sustained following completion of treatment and complement clinical trial evidence of improved pain-related QoL.

Novel strategies and agents in development:
Results presented with novel agents and strategies, while positive, are not practice changing in Canada at this time.
- In the current treatment landscape where most patients with mCSPC are patients being treated with an ASI up front, the clinical question of adding abiraterone to docetaxel is simply not as relevant as when PEACE-1 was designed.
- Longer follow-up is needed to better characterize clinical benefits of adding NIVO to rucaparib in CT-naive mCRPC.

SEE MORE INSIGHTS AND REVIEWS OF SELECT TRIALS COVERED IN THIS REPORT FROM DR. ALAN SO

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