Research Review™
SPEAKER SERIES
Advances in the Management of Metastatic Prostate Cancer
Making Education Easy 2022

About the speakers

Professor Lisa Horvath

Lisa Horvath is the inaugural Director of Research at Chris O'Brien Lifehouse. Prior to heading up the research department, Lisa was the Director of Medical Oncology at Royal Prince Alfred Hospital for seven years before transitioning the service to Chris O'Brien Lifehouse where she remained at the helm for another seven years. Lisa is the conjoint Professor of Medical Oncology (Genitourinary cancer) at the University of Sydney. She is also a member of Faculty at the Garvan Institute of Medical Research and Head of Advanced Prostate Cancer research group.

Professor Fred Saad

Fred Saad is Professor and Chairman of Urology and Director of Genitourinary Oncology at the University of Montreal Hospital Center (CHUM) in Montreal, QC, Canada. He holds the Raymond Garneau Chair in Prostate Cancer Research and is Director of Clinical Research and the Molecular Oncology Research Laboratory in Prostate Cancer. Prof. Saad's research interests include novel therapeutics in prostate cancer, molecular prognostic markers, and mechanisms of progression. He has over 40 clinical and basic research projects ongoing and has received over $CAD40 million in research grants. Prof. Saad currently sits on 15 steering committees of ongoing international clinical trials and serves on several guideline committees.

Panel

Associate Professor Ben Tran
Consultant, Peter MacCallum Centre and Walter and Eliza Hall Institute of Medical Research, Melbourne

Associate Professor Louise Emmett
Director, Theranostics and Nuclear Medicine, St Vincent's Hospital, Sydney

Professor Jarad Martin
Director, Lake Macquarie Private Hospital, Genesis Cancer Care, Newcastle

Dr Renu Eapen
Consultant, Peter MacCallum Cancer Centre and Austin Hospital and Olivia Newton-John Cancer Centre, Melbourne

This Amgen-sponsored webinar was presented on May 18th, 2022 and involved two speakers' presentations, followed by a panel discussion chaired by Dr Ben Tran and involving multidisciplinary prostate cancer experts who discussed the topics covered. In the first presentation, Professor Lisa Horvath provided an outline of the recent advances in the management of patients with newly diagnosed metastatic hormone-sensitive prostate cancer. The second presentation by Professor Fred Saad focused on metastatic castrate-resistant prostate cancer and the advances in the management of these patients.

Advances in metastatic hormone-sensitive prostate cancer

Professor Lisa Horvath

Introduction

The management of metastatic hormone-sensitive prostate cancer (mHSPC; see **Table 1** for definitions) has changed dramatically in the last 10 years.[1, 2] Historically, men with mHSPC have been treated with androgen deprivation therapy (ADT), but changes in the management of these patients have resulted in improved survival outcomes.

Table 1. Definitions of high volume and low volume metastatic hormone-sensitive prostate cancer (mHSPC)[3, 4]

Category	Definition
High volume mHSPC	Meets 1 or both criteria (CHAARTERED definition)[3] • ≥4 bone lesions on bone scan (at least 1 outside vertebrae/pelvis) • Measurable visceral metastases
	Meets 2 out of 3 criteria (LATITUDE definition)[4] • ≥3 bone metastases • Gleason score ≥8 • Measurable visceral metastases
Low volume mHSPC	Meets 1 or both criteria • Lymph node only disease outside the pelvis • 3 or less bone lesions on bone scan
Oligo-metastatic HSPC	Limited metastatic sites

How do we use PSMA-PET scan results?

There are a lot of questions around the role of Prostate-Specific Membrane Antigen (PSMA)-positron emission tomography (PET) scans, given the fact that most randomised control trials have used conventional imaging (CIM) rather than PSMA-PET to assess the extent of the disease.[5] To provide clarity around the management of patients according to imaging findings, an international, multidisciplinary group of prostate cancer experts have developed an algorithm (**Figure 1**).[5]

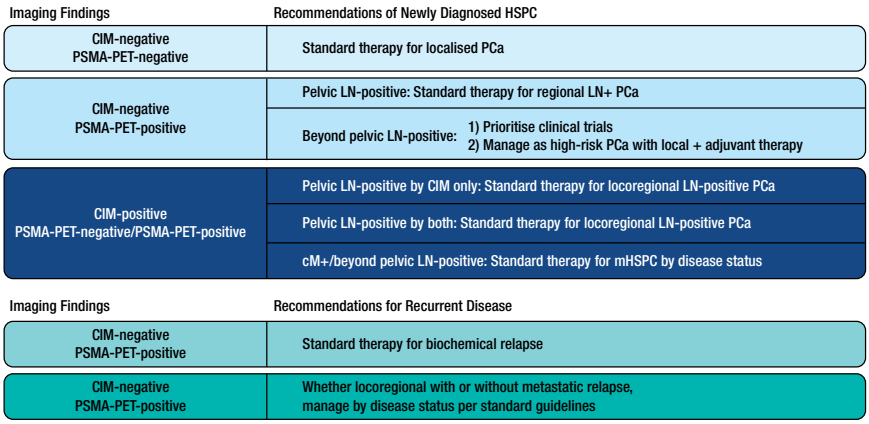

Figure 1. Management recommendations based on positive/negative imaging for metastases on conventional imaging (CIM) and prostate-specific membrane antigen-positron emission tomography (PSMA-PET) scans[5]
HSPC = hormone-sensitive prostate cancer; **LN** = lymph node; **mHSPC** = metastatic hormone-sensitive prostate cancer; **PCa** = prostate cancer.

In patients with newly diagnosed HSPC, if both conventional imaging and PSMA-PET scans are negative, standard therapy should be used.[5] But if CIM is negative, but PSMA-PET is positive, the algorithm suggests that patients with regional pelvic lymph node positive disease should receive standard therapy.[5] If CIM is negative, but PSMA-PET is positive, and there is pelvic lymph node involvement, retroperitoneal lymph node involvement, and possibly a bone metastasis, then more intensive treatment is recommended.[5]

Types of intensive treatment in mHSPC

Combining novel therapies with ADT at the time of initiating systemic therapy for mHSPC has been developed as a strategy to delay the development of castrate-resistant prostate cancer (CRPC) and improve health-related quality of life (HR-QoL) and overall survival (OS).

Docetaxel + ADT

The addition of docetaxel to ADT in men with mHSPC compared with ADT alone improved OS, as shown in the CHAARTED (Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial in men with high volume disease (hazard ratio [HR] 0.63; 95% CI 0.50, 79; p<0.001) and in the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial in both high (HR 0.81; 95% CI 0.64, 1.02) and low volume disease (HR 0.76; 95% CI 0.54, 1.07), and across both low and high volume patients combined (HR 0.80; 95% CI 0.69, 0.95; p=0.0009) respectively.[6, 7]

AR signalling inhibitors + ADT

More recent clinical trials have also supported the additional use of androgen receptor (AR) signalling inhibitors (e.g., abiraterone, enzalutamide, or apalutamide) with ADT, compared with ADT alone, in the treatment of mHSPC with OS HRs generally in the range of 0.6 (apart from ARCHES with 0.39).[8-11] In these studies, the addition of AR signalling inhibitors to ADT was effective in both high volume and low volume disease.[11]

Studies involving men with mHSPC have investigated triplet systemic treatment with ADT, chemotherapy, and an AR signalling inhibitor (**Table 2**).[12-16] The ARCHES and TITAN study used docetaxel prior to the addition of an AR signalling inhibitor, and only in a small proportion of patients, so outcomes in this patient group are difficult to interpret.[14, 15] However, in the PEACE-1,[12] ARASENS,[16] and ENZAMET[13] studies, docetaxel was given concurrently with the AR signalling inhibitor. Data from the PEACE-1[12] and the ARASENS[16] have reported improvements in OS with the triple therapy compared with ADT plus chemotherapy. Survival outcomes from the ENZAMET study are expected in coming months.

Table 2. Triplet systemic therapy in men with metastatic hormone-sensitive prostate cancer

Trial	Total cohort N	Docetaxel treated (% pts)	Investigational agent	Timing of docetaxel	Outcome
PEACE-1[12]	1172	710 (60)	Abiraterone	Concurrent	Improved rPFS, improved OS in HV
ENZAMET[13]	1125	503 (45)	Enzalutamide	Concurrent	Improved rPFS, no change in OS (immature data)
TITAN[14]	1052	113 (10)	Apalutamide	Prior	NA
ARCHES[15]	1150	205 (17)	Enzalutamide	Prior	NA
ARASENS[16]	1300	1300 (100)	Darolutamide	Concurrent	Improved rPFS and OS

HV = high volume disease; **NA** = not available; **OS** = overall survival; **rPFS** = radiographic progression-free survival.

PEACE-1 study

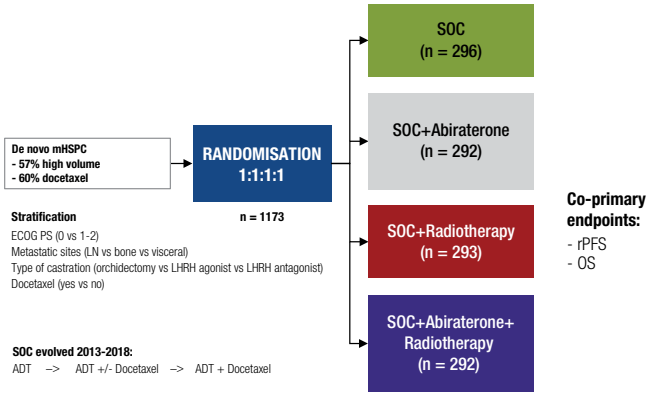

Figure 2. Study design of the PEACE-1 study[12]
ADT = androgen-deprivation therapy;
ECOG PS = Eastern Cooperative Oncology Group performance status;
LHRH = luteinizing hormone-releasing hormone; **mHSPC** = metastatic hormone-sensitive prostate cancer;
OS = overall survival; **rPFS** = radiologic progression-free survival; **SOC** = standard of care.

In the multicentre, randomised, open-label PEACE-1 study (with a 2 x 2 factorial design) men with *de novo* mHSPC (57% of the men had high volume disease) were randomised (1:1:1:1) to standard of care (SOC), SOC plus radiotherapy, SOC plus abiraterone (oral abiraterone plus prednisone), or SOC plus radiotherapy plus abiraterone (**Figure 2**).[12] The SOC evolved over the course of the study; initially with ADT alone, then ADT with the optional addition of docetaxel, then in the later part of the study ADT plus docetaxel was mandatory.[12] The co-primary endpoints were radiographic progression-free survival (rPFS) and OS.[12] In the group of men who received SOC plus or minus abiraterone, rPFS was longer with abiraterone plus SOC, compared with those who received SOC alone, both in those with both low volume disease (HR 0.58; 95% CI 0.39, 0.87; p = 0.006) and in those with high volume disease with an improvement in HR (0.47; 95% CI 0.36, 060; p<0.0001).[12, 17] OS was significantly different between the two treatment arms in patients with high volume disease, with an improvement of over 18 months in those treated with triplet therapy (HR 0.72; 95% CI 0.55, 0.95; p=0.019). In men with low volume disease, the difference between the two treatment groups was not significant, but further follow-up is needed in this setting.

ARASENS study

The international, double-blind, phase 3 ARASENS trial was conducted in 1306 men with mHSPC; however, this time the SOC was defined up front as ADT with docetaxel. Patients were randomised to receive darolutamide plus SOC (651 patients) or placebo plus standard of care (655 patients) (**Figure 3**).[16] Patients had to be candidates for ADT plus docetaxel.

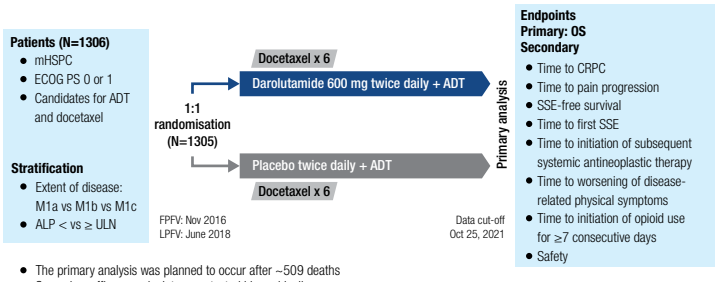

Figure 3. Study design of the ARASENs trial[16]
ADT = androgen-deprivation therapy; **ALP** = alkaline phosphatase levels;
CRCP = castration-resistant prostate cancer;
ECOG PS = Eastern Cooperative Oncology Group performance status; **FPFV** = first patient first visit;
LPFV = last patient first visit; **mHSPC** = metastatic hormone-sensitive prostate cancer;
OS = overall survival; **SSE** = symptomatic skeletal event; **ULN** = upper limit of normal.

The primary endpoint was OS.[16] Patients had relatively advanced disease; 86.1% of the patients had disease that was metastatic at the time of the initial diagnosis, the majority had bone metastases (79.4% to 79.5%), 17% to 18% had visceral metastases, and more than 75% of the patients have a Gleason score ≥8.[16]

There was a significant improvement in OS with the triplet combination compared with the doublet combination (HR 0.68; 95% CI 0.57, 0.80; p<0.001: **Figure 4**).[16]

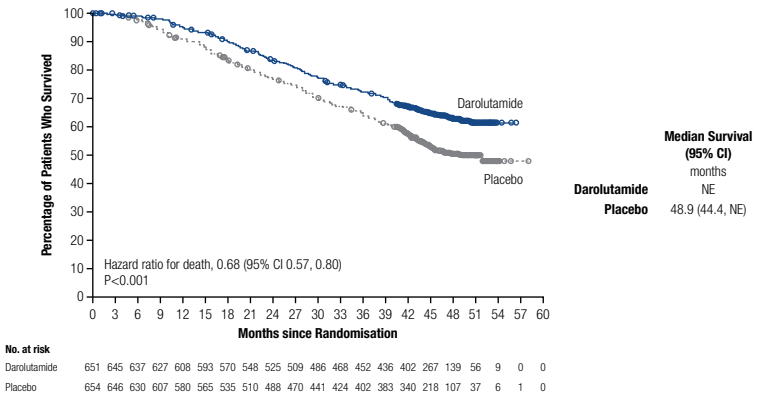

Figure 4. Overall survival in the ARASENs trial[16]
CI = confidence interval; **NE** = not evaluable.

In addition, the time to castration-resistance disease was also significantly longer with the triple combination than with ADT plus docetaxel alone (not evaluable vs 19.1 months; HR 0.36; 95% CI 0.30, 0.42; p<0.001).[16] There was very little added toxicity with the triple combination compared with the doublet combination.[16]

Summary: treatment of mHSPC

In summary, Professor Horvath stated that patients with mHSPC with high volume disease can be treated with ADT plus docetaxel or an AR signalling inhibitor (e.g., abiraterone, enzalutamide, or apalutamide). In those with synchronous high volume, good performance status, then ADT plus docetaxel plus concurrent abiraterone or darolutamide can be administered.

In patients with low volume mHSPC, ADT plus radiotherapy to the primary lesion (if *de novo*) plus ideally systemic treatment with an AR signalling inhibitor could be administered.

Case study one: Synchronous high volume metastatic prostate cancer

Mr NA is a male aged 63 years, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0. He was working fulltime and had children in high school. His previous medical history was limited to gout and hypertension. He presented with nocturia, rectal pain, and a prostate specific antigen (PSA) of 60. Magnetic resonance imaging (MRI) indicated that he had locally advanced prostate cancer invading the pelvic floor and into the nerve bundles. A PSMA-PET scan revealed a prostate mass, with bilateral pelvic lymph node uptake, and 20 liver metastases. A prostate biopsy gave a Gleason score of 9 and an International Society of Urological Pathology (ISUP) grade of 5.

Treatment:
The patient was treated with Lucrin (leuprorelin acetate) plus docetaxel plus self-funded abiraterone. His PSA is now 1.7 at the end of docetaxel treatment, and he has shown a partial response on a CT scan.

Case 2: Synchronous low volume metastatic prostate cancer

Mr IC is a male aged 72 years, with a ECOG PS of 0. He had primary artery bypass surgery 10 years ago and he has hypertension. A routine PSA level was 20. On MRI, a Prostate Imaging Reporting and Data System (PI-RADS) score 5 lesion was identified, on biopsy he had a Gleason score of 8, and a PSMA-PET scan revealed a prostate mass, 3 bony lesions (T11 and 2 ribs), and sclerosis in T11 and in 1 rib on a computed tomography (CT) scan.

Treatment:
The patient was treated with Lucrin (leuprorelin acetate) plus radiotherapy to the prostate and he now has a PSA of 0.19. Given the funding issues of treatments in Australia, treatment with an AR signalling inhibitor must be self-funded through the access programme ($1700 per month). This patient could also be treated with stereotactic body radiation therapy, but given the lack of consensus around this scenario, this option was not offered to the patient.

Maintaining HR-QOL in patients with mHSPC

Since patients with mHSPC are living much longer, it is vital that their HRQoL is maintained, Professor Horvath stated.

A review of data from the SEER database in more than 50,000 men with prostate cancer found there was a statistically significant relationship between the number of doses of ADT received during the 12 months after diagnosis of prostate cancer and the risk of bone fracture.[18] Data from a randomised, controlled trial showed that treatment of non-metastatic HSPC patients with denosumab significantly increase the bone mineral density at all skeletal sites.[19] Importantly, although the patient numbers were low, the fracture rate was also decreased. Patients who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5% vs 3.9% with placebo; relative risk, 0.38; 95% CI 0.19, 0.78; p=0.006).[20]

Professor Horvath commented that keeping men with mHSPC healthy for the years they live with the disease will involve assessing their risk factors (e.g., with a geriatric risk assessment if there is insipient frailty, consideration of cardiovascular risk factors, and regular DEXA bone mineral density scans). Interventions that can be recommended include exercise, the use of bone protection agents (calcium/vitamin D with or without denosumab or zoledronic acid), and reducing cardiovascular risk factors.

A study in patients with non-metastatic castrate-resistant prostate cancer (nmCRPC) indicated that >90% of patients had evidence of metastases on a PSMA-PET scan, even without any evidence on conventional imaging.[21] In the STAMPEDE study, which used conventional imaging, men who present with an intact prostate with high risk localised disease were treated with radiotherapy to the primary lesion and two years of intensified treatment with ADT plus abiraterone plus prednisolone (AAP) ± enzalutamide, or alternatively treatment with ADT alone.[22] With AAP-based therapy, there was a six-year metastasis-free survival improvement from 69% to 82% and a 6-year improvement in OS from 77% to 86%.[22]

Professor Horvath noted that patients with synchronous low volume mHSPC, diagnosed on PSMA-PET scan (especially those patients with three retroperitoneal lymph nodes or supraclavicular fossa lymph nodes) would be diagnosed as M0 locally advanced prostate cancer by conventional imaging. She commented that if these patients are treated as having low volume disease, they might receive continuous ADT for the rest of their lives. Professor Horvath suggested that potentially these patients should be treated with radiotherapy plus ADT plus abiraterone for two years only given the increased length of time these men may be alive.

Who should receive intensive treatment in mHSPC?

The ENZAMET study indicated that in the first 12 months of treatment, there is a group of men who relapse, including those treated with intensive therapy with enzalutamide.[13] Similarly, at 18 months, there is also a group of men who die.[13] Conversely, beyond the 3 years, there is a group of men who have not relapsed, even if treated with ADT alone. In order to determine the characteristics of these groups, the STOPCAP M1 group are investigating the clinical risk stratification (good risk, intermediate risk, poor risk) of men likely to develop localised prostate cancer, based on bone metastases, liver metastases, the presence of synchronous metastatic disease.[23]

Professor Horvath commented that molecular profiling is also as important. The ENZAMET study is evaluating tissue and blood samples from patients to identify biomarkers that are prognostic and/or predictive of response to treatment. Prospective biomarkers being evaluated include circulating DNA, tissue DNA and RNA, cytokines, and lipid metabolism. In addition, mutations in tumour suppressor genes, such as TP53, PTEN, and RB1, have been associated with a greater risk of aggressive prostate cancer.[24, 25]

Conclusion

Professor Horvath summarised the various therapeutic options available for the treatment of prostate cancer in 2022 (**Figure 5**).

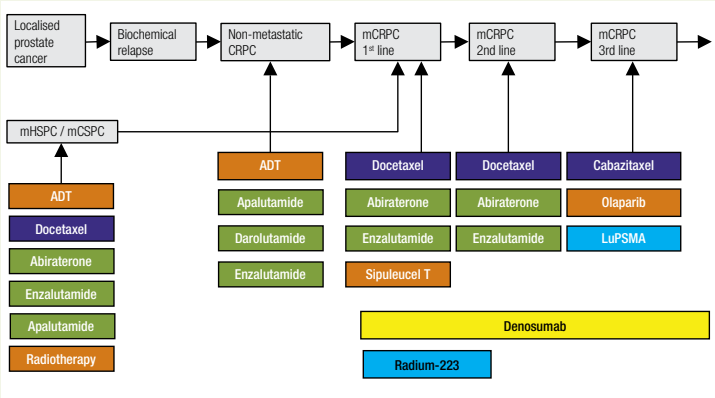

Figure 5. Therapeutic options available for the treatment of prostate cancer in 2022
CRPC = castrate-resistant prostate cancer; **mCRPC** = metastatic castrate-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer.

It has been an extraordinary "two decades of progress in this field" and it is "a really good time for our patients because they are living longer and with a better quality of life", concluded Professor Horvath.

Q&A discussions

A person with high volume *de novo* prostate cancer presents with severe bony pain. How should their painful pelvic mass be treated?

Professor Jarad Martin: Sometimes if a patient is treated with ADT and docetaxel, and there is a good response with the PSA diminishing, this may result in an effective analgesic outcome, with simple analgesia used to treat any emergent pain. However, in patients with severe debilitating bony pain, the key is to engage a multidisciplinary team who can develop a coherent care plan for the patient.

Professor Fred Saad: Most patients will respond well to early systemic therapy, but in the rare instances of patients who are at risk of bone fracture, radiation or orthopaedic departments may be involved. In such patients, we might use an androgen receptor antagonist to lower the testosterone levels as quickly as possible.

Should we use systemic therapy and radiation in patients with oligometastatic disease?

Professor Lisa Horvath: Patients who present with mHSPC need systemic treatment – you cannot just treat what you can see; you have to treat what you cannot see. Regarding metastatic-directed radiation therapy in patients treated with systemic therapy, the benefit is not clear as outcomes from randomised trials involving this patient group have not been published. Having a registry of these patients, would at least enable us to follow this group.

Professor Fred Saad: A Canadian randomised clinical trial involving patients with oligometastatic disease is currently being conducted to compare best systemic therapy with or without metastatic-directed therapy (guided by conventional imaging plus PSMA-PET).

Professor Jarad Martin: Whether to provide radiation to the prostate for patient with limited metastatic prostate cancer can be nuanced. For example, in a patient with early, high-volume disease (5 metastases), but with a locally advanced primary prostate cancer (T4) that is invading into the pelvic floor in the rectum, you might consider radiation to the prostate.

Should exercise receive the same prescribing imperative as drug therapy?

Professor Jarad Martin: Exercise is associated with numerous benefits when engaged in alongside with chemotherapy, radiotherapy, and surgery. Exercise activates the immune system, it makes patients feel better, it reduces the toxicities of drugs, and it is something that patients can take ownership of. As oncologists, we should be "cheerleaders" for exercise and encourage our patients to get involved in some of the numerous forms of exercise provided by exercise physiologists or that are available in the community.

Professor Lisa Horvath: I think we need to acknowledge that some people find exercise boring, so exercise needs to be personalised. A distraction (e.g., listening to an ebook, or music) while exercising may be beneficial for some patients.

Dr Renu Eapen: As oncologists, we need to lead by example. Exercise is an important aspect of care that we need to discuss with our patients, particularly those with metastatic prostate cancer.

Professor Fred Saad: GAP4, a multicentre, randomised, controlled, phase 3 study is currently being conducted to determine if supervised high-intensity aerobic and resistance training increases overall survival compared to self-directed exercise in patients with metastatic prostate cancer.[25] Positive outcomes from this trial would enable physicians to present evidence to patients that exercise enables them to live longer.

Dr Ben Tran: GAP4 is a Movember initiative that is available through sites in Australia.

A patient who is fit and well, and aged 70 years presents with *de novo*, low volume mHSPC. He has had radiation to the prostate, hormonal therapy (ADT), but cannot afford abiraterone therapy. He is discussing docetaxel with his oncologist, and was found to have a *BRCA2* mutation. How should he be treated?

Professor Lisa Horvath: In patients with metastatic, hormone-sensitive, lymph node only prostate cancer, there are not enough data to warrant treatment with docetaxel in most instances. The presence of a *BRCA2* mutation is not going to change how I would treat this patient in the first-line setting, but he would be carefully followed at regular intervals because he is more likely to have early failure after ADT, and will require other therapies such as a PARP inhibitor.

Professor Louise Emmett: I would definitely not use lutetium-177-PSMA in this patient. Lutetium-177-PSMA is effective following docetaxel in patients with end-stage disease in whom prostate-specific membrane antigen (PSMA) is highly expressed in mCRPC lesions. However, research still needs to be completed to determine the efficacy and tolerability of lutetium-177-PSMA in patients with mHSPC in whom PSMA may not be so extensively expressed.

What treatment options are available for patients with mHSPC who eventually become castrate resistance after extensive treatment with triplet therapy (e.g., ADT plus docetaxel plus concurrent abiraterone)?

Professor Fred Saad: With more extensive treatment, patients with mHSPC are living longer before they become castrate resistant. We still have options for these patients: they could be treated with cabazitaxel or lutetium-177-PSMA (based on imaging), and molecular profiling may reveal mutations in DNA repair pathways (e.g. *BRCA* mutations) that can be targeted with drug therapy. In patients with disease that has progressed after a number of lines of therapy, we need to identify biomarkers that can be targeted so that we can understand what we are actually treating.

Professor Lisa Horvath: In terms of identifying if a patient with mHSPC has a *BRCA* mutation, I tend to wait about 6 months after diagnosis (once they are responding to treatment) – so early but not too early. *BRCA* mutation assessment, should be standard of care, and it now has a Medicare Benefits Schedule item number for somatic and germline testing.

Professor Louise Emmett: In castrate-resistant patients, imaging is a biomarker. In the future, molecular imaging, such as PSMA-PET, is going to become increasingly important in our decision-making about suitable treatment.

Optimally managing metastatic castrate-resistant prostate cancer

Professor Fred Saad

Evidence from Phase 3 trials

Metastatic castrate resistant prostate cancer (mCRPC) is the only state of the disease that patients die **of** prostate cancer, rather than **with** prostate cancer, Professor Saad commented.

In the phase 3 trials that have been conducted in men with mCRPC (**Table 3**), although the improvement in OS is modest (2-5 months) with the various therapies investigated, the survival rate is about twice the survival with docetaxel alone.[26-34] Professor Saad commented that the drugs used in men with mCRPC have been tested either against placebo, or an ineffective control. This means that moving forward, if OS is used as the endpoint, trials will have to enrol large number of patients if very effective life prolonging control arms are used. For example, the PREVAIL trials, enrolled over 1700 patients to indicate that enzalutamide compared with placebo was associated with a survival advantage.[29] Professor Saad suggested that other surrogate endpoints will need to be used instead of OS to investigate new therapeutic options.

Table 3. Phase 3 trials in men with metastatic castrate resistant prostate cancer

Study	Agents	N	Indication	HR	Change in OS (months)
TAX-327[26]	DOC/P vs mito/P	1006	mCRPC, symptomatic or not	0.76	+2.9
COU-AA-302[27]	ABI/P vs P	1088	mCRPC (pre-DOC), mild / no symptoms No visceral metastases	0.81	+4.4
COU-AA-301[28]	ABI/P vs P	1195	mCRPC (post-DOC)	0.74	+4.6
PREVAIL[29]	ENZ vs PBO	1717	mCRPC (pre-DOC), mild / no symptoms	0.77	+4.0
AFFIRM[30]	ENZ vs PBO (or P)	1199	mCRPC (post-DOC)	0.63	+4.8
TROPIC[31]	CABA/P vs mito/P	755	mCRPC (post-DOC)	0.70	+2.4
ALSYMPCA[32]	Radium-223 vs PBO	921	mCRPC (post-DOC or unfit for DOC)	0.70	+3.6
PROfound[33]	Olaparib vs NHT	245	mCRPC post-NHT (with HRRm)	0.69	+4.4
VISION[34]	Lu-PSMA vs NHT	831	mCRPC post-NHT (with PSMA+) and chemo	0.62	+4.0

ABI = abiraterone; **CABA** = cabazitaxel; **chemo** = chemotherapy; **DOC** = docetaxel; **ENZ** = enzalutamide; **HR** = hazard ratio; **HRRm** = homologous recombination repair gene mutation; **Lu-PSMA** = lutetium-177 prostate-specific membrane antigen; **mCRPC** = metastatic castration-resistant prostate cancer; **mito** = mitoxantrone; **mo** = months; **NHT** = neoadjuvant hormonal therapy; **OS** = overall survival; **P** = prednisone; **PBO** = placebo.

Does earlier treatment improve outcomes?

Studies support the concept that earlier treatment improves outcomes. For example, in the COU-AA-302 trial involving abiraterone treatment, patients with lower PSA scores did much better than those with higher PSA (**Table 4**).[27] Professor Saad emphasised that early referrals to the medical oncologist is important for prolonging survival. Other parameters that predicted an OS advantage with abiraterone included baseline ECOG, pain, and alkaline phosphatase values.[27, 35]

Table 4. Survival outcomes in patients with different baseline PSA values in the COU-AA-302 trial[27]

Quartile	Q1	Q2	Q3	Q4
Baseline PSA (ng/mL)	<15.6	15.6 to <39.5	39.6 to <106.2	≥106.2
		Overall survival		
HR (95% CI)	0.53 (0.39, 0.72)	0.71 (0.54, 0.93)	0.87 (0.67, 1.11)	1.00 (reference)
P value	<0.001	0.014	0.257	-

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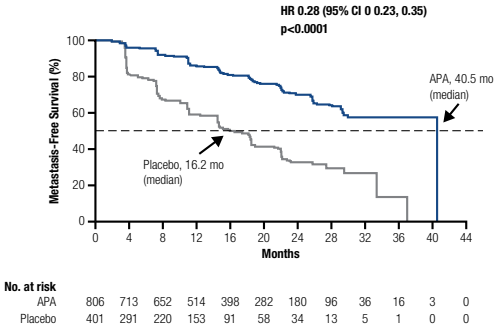
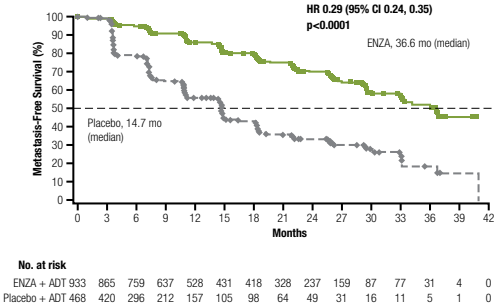
Professor Saad commented that the main argument that earlier is better comes from studies involving patients with very low volume metastatic CRPC (classified as non-metastatic CRPC [nmCRPC] when using conventional imaging). In this group of patients, AR targeted therapy (e.g., with apalutamide, enzalutamide, or darolutamide) was effective in prolonging the primary endpoint of metastatic-free survival (MFS; assessed on conventional imaging: **Figure 6**).[36-38] In this group of high-risk prostate cancer patients, AR-targeted therapy delayed the development of metastases (on conventional imaging) by about 2 years.[36-38] No difference between the treatment groups was observed in OS (partially because the placebo arm patients were treated with the AR-targeted therapy when metastases appeared).

SPARTAN (Apalutamide)



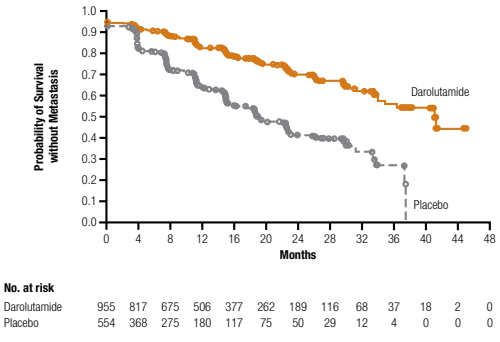
- 72% reduction of metastases or death
- 40.5 months vs Placebo 16.2 months
- **24-month additional MFS**

PROSPER (Enzalutamide)



- 71% reduction of metastases or death
- 36.6 months vs 14.7 months
- **22-month additional MFS**

ARAMIS (Darolutamide)



- 59% reduction of metastases or death
- 40.4 months vs 18.4 months
- **22-month additional MFS**

Figure 6. Metastatic-free survival in men with non-metastatic castrate-resistant prostate cancer, with a PSA doubling time (PSAD) of ≤10 months in the SPARTAN,[36] PROSPER,[37] and ARAMIS[38] trials

APA = apalutamide; **CI** = confidence interval; **ENZA** = enzalutamide; **HR** = hazard ratio; **MFS** = metastatic-free survival.

Early treatment with AR-targeted agents delayed the time to resistance (**Figure 7**). PSA progression occurred much later if patients with nmCRPC are started on an AR-targeted agent in the non-metastatic setting.[29, 39-41] In the metastatic setting, the later the treatment with AR-targeted therapy in the disease course of men with nmCRPC, then the sooner resistance developed.[36-38]

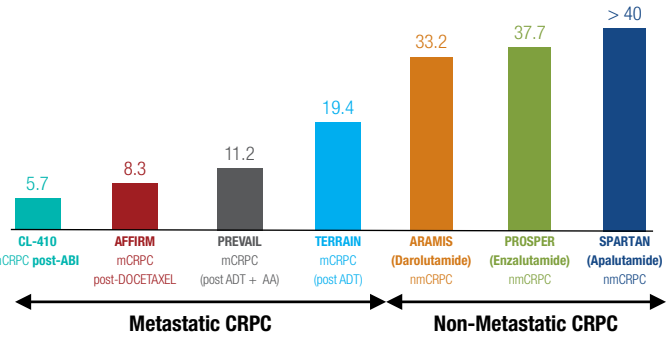
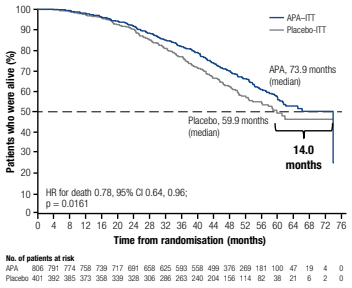


Figure 7. Time (months) to prostate-specific antigen progression in the CL-410,[39] AFFIRM,[40] PREVAIL,[29] TERRAIN,[41] ARAMIS,[38] PROSPER,[37] and SPARTAN[36] trials in patients treated with AR-targeted therapy

ABI = abiraterone; **ADT** = androgen deprivation therapy; **mCRPC** = metastatic castrate-resistant prostate cancer; **nmCRPC** = non-metastatic metastatic castrate-resistant prostate cancer.

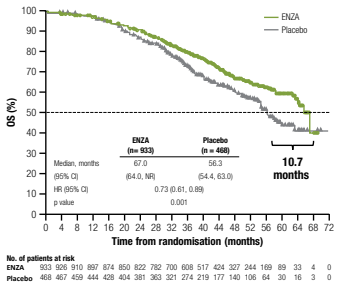
Final analysis of the SPARTAN,[36] PROSPER,[37, 42] and ARAMIS[38, 43] trials indicated a significant OS advantage of about 1 year for men with nmCRPC treated with AR-targeted therapy, in spite of the placebo recipients receiving treatment at the first sign of metastases (**Figure 8**). The survival outcomes were about 2-3 times greater in this micro-metastatic setting, than when these drugs were started in a mCRPC, Professor Saad commented.

SPARTAN



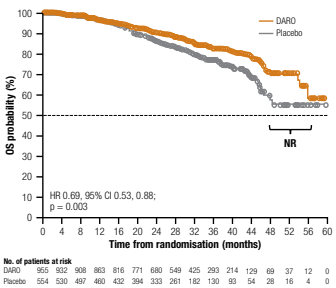
OS events:
- APA 274 (34%) and Placebo 154 (38%)

PROSPER



OS events:
- ENZA 288 (31%) and Placebo 178 (38%)

ARAMIS



OS events:
- DARO 144 (16%) and Placebo 106 (19%).

Figure 8. Overall survival in the final analysis of the SPARTAN,[36, 44] PROSPER,[37, 42] and ARAMIS[38, 43] trials

APA = apalutamide; **CI** = confidence interval; **DARO** = darolutamide; **ENZA** = enzalutamide; **HR** = hazard ratio; **NR** = not reported; **OS** = overall survival.

Is the PSA response to therapy relevant?

Once the AR-targeted agents are started, PSA response becomes the best predictor of survival, Professor Saad commented.[45] In the SPARTAN study, early onset and depth of a PSA response were associated with long-term benefits (MFS and OS) of apalutamide in patients with nmCRPC (**Figure 9**).[45]

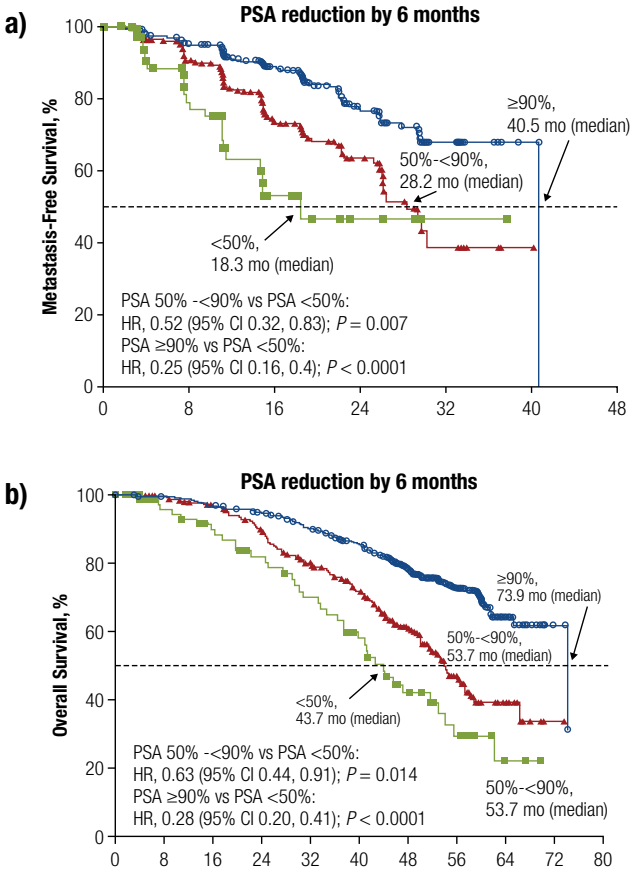


Figure 9. a) Metastatic-free survival and b) overall survival according to PSA reduction (≥90%, 50%-<90%, <90%)[45]
CI = confidence interval; **HR** = hazard ratio; **PSA**= prostate-specific antigen.

HR-QOL (assessed according to the Functional Assessment of Cancer Therapy-Prostate score) was maintained with all three drugs (**Figure 10**), which is extremely important in these asymptomatic patients, Professor Saad commented.[38, 46, 47]

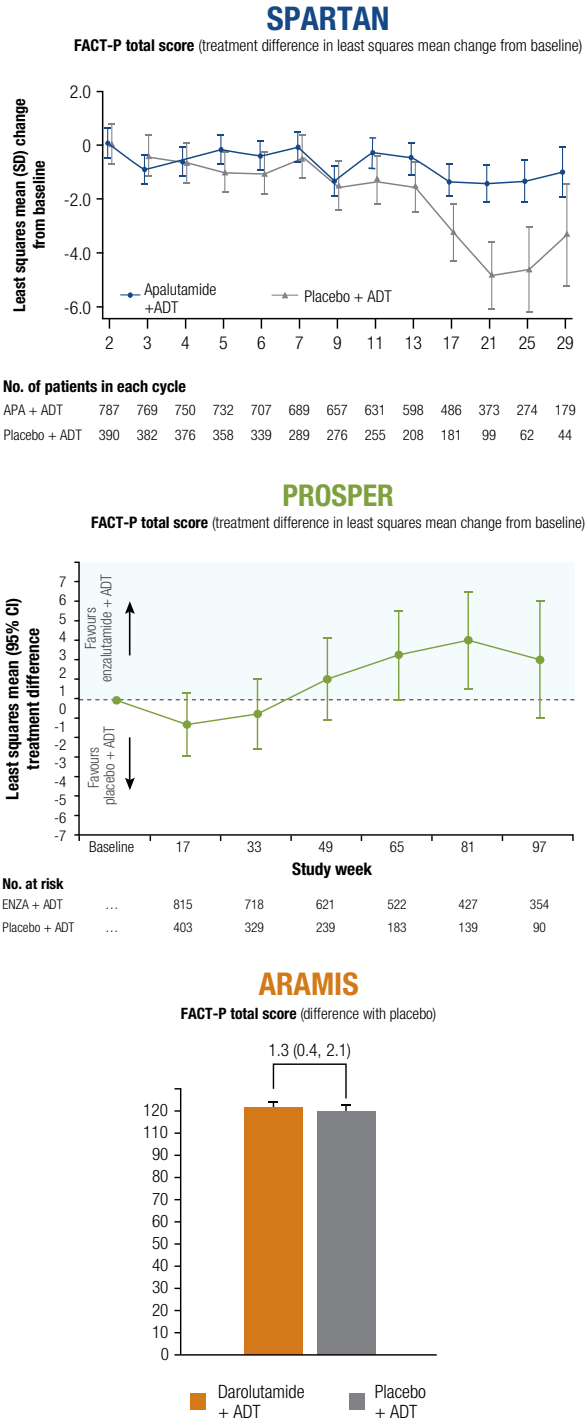


Figure 10. Functional Assessment of Cancer Therapy-Prostate (FACT-P) in men with non-metastatic castration-resistant prostate cancer in the SPARTAN,[46] PROSPER,[47] and ARAMIS[38] trials
ADT = androgen deprivation therapy; **APA** = apalutamide.

Outcomes from novel imaging should not change our approach in high-risk nmCRPC in terms of systemic therapy,[5] Professor Saad argued. High-risk nmCRPC patients with a single lesion on PET/CT could be targeted with radiation therapy **plus** systemic therapy, Professor Saad noted. But in the low-risk patient, with a slow rising PSA, and no indication for intensive systemic therapy, then maybe targeting the oligometastatic lesion could make a difference in delaying the need for expensive systemic therapy in the nmCRPC patient, Professor Saad commented. When PSMA-PET is carried out in high-risk patients, metastatic lesions were seen in 98% of patients.[21] Professor Saad commented that the question of whether targeting these lesions makes a difference in patients with rapidly rising PSA still needs to be addressed.

Personalising treatment options

A significant proportion of patients with mCRPC harbour mutations in DNA repair pathways, which can be targeted with drug therapy,[48-50] commented Professor Saad.

PROfound study

The randomised, open-label, phase 3 trial PROfound study was conducted in patients with mCRPC who had disease progression while receiving a new hormonal agent (e.g., enzalutamide or abiraterone) irrespective of their having received treatment with chemotherapy, and who had an alteration in at least one gene with a direct or indirect role in homologous recombination repair (HRR; e.g., *BRCA1/2, or ATM*).[33, 51] Over 4000 men were screened, with just under 400 men being eligible for entry into the study based on identification of the genes in the tumour tissue. Patients were randomly assigned (2:1) to receive the poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitor olaparib or the physician's choice of enzalutamide or abiraterone (control). Patients in the control arm crossed overed to olaparib when they progressed, so at some point all patients received olaparib.[51] In patients with *BRCA1/2* or *ATM* mutations treated with olaparib, compared with enzalutamide or abiraterone, there was a significant reduction in the risk of progression or death by 66% in patients and a 31% reduction in the risk of death (**Figure 11**).[33] Importantly, the advantage with olaparib occurred even though patients in the control group were allowed to crossover to olaparib on progression of disease.[33] This outcome indicates that earlier introduction of olaparib in a patient with a *BRCA* mutation is better than delaying its introduction, commented Professor Saad. If this was not the case, then the patients on the control arm should have caught up in terms of OS, noted Professor Saab. Adjusting for crossover, resulted in a 58% reduction risk of death.[33] The median time to pain progression was significantly longer in the olaparib group than in the control group (HR 0.44; 95% CI 0.22, 0.91; p=0.02) and HR-QoL was improved in more patients treated with olaparib than in the control group.[33, 52]

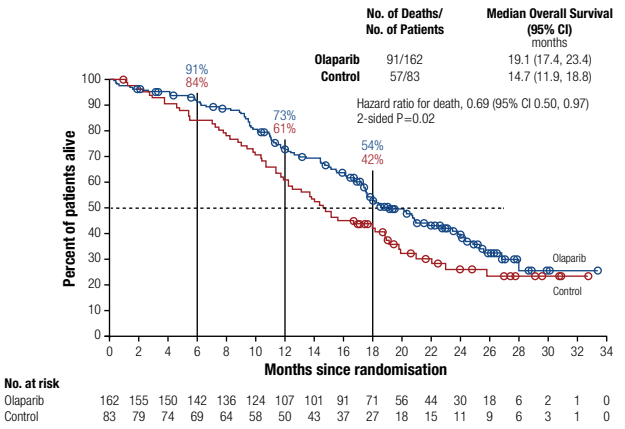


Figure 11. Overall survival in the PROfound trial in patients with mCRPC treated with olaparib compared with physician's choice of enzalutamide or abiraterone (control)[33]

PROpel study

In the phase 3, double-blind PROpel trial, patients with mCRPC with ongoing ADT were randomly assigned to receive first-line treatment with olaparib plus abiraterone or placebo plus abiraterone (an active control) (**Figure 12**).[53] Trial participants were not selected according to HRR mutations, but 28-29% harboured detectable mutations.

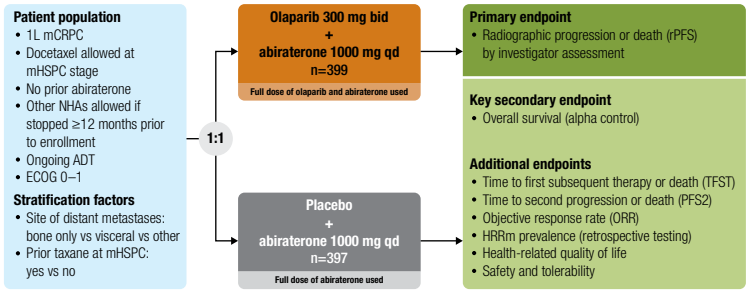


Figure 12. Study design of the PROpel study[53]
ADT = androgen-deprivation therapy; **bid** = twice daily;
mCRCP = metastatic castration-resistant prostate cancer;
ECOG PS = Eastern Cooperative Oncology Group performance status; **HRR** = homologous recombination repair;
mHSPC = metastic hormone sensitive prostate cancer; **NHAs** = new hormonal agents; **qd** = once daily.

Median rPFS was improved by about 8 months with olaparib plus abiraterone compared with abiraterone alone (according to investigator assessment) and by about 11 months by blinded independent central review (BICR) (**Figure 13**).[53] There was also a 34% risk reduction for progression or death with olaparib plus abiraterone compared with abiraterone alone (HR 0.66; 95% CI 0.54, 0.81; p<0.0001).[53] Moreover, all prespecified subgroups benefited from the addition of olaparib to abiraterone, including those with HRR mutations and those without HRR mutations, and those aged <65 years and those aged ≥65 years. OS data are immature.[53] The olaparib combination was well tolerated in this group of patients who had not been pre-exposed;[53] the most common grade ≥3 adverse event reported was anaemia (15.1% vs 3.3%) for olaparib plus abiraterone compared with abiraterone alone.[53] All other grade ≥3 adverse events were reported in <5% of patients.[53]

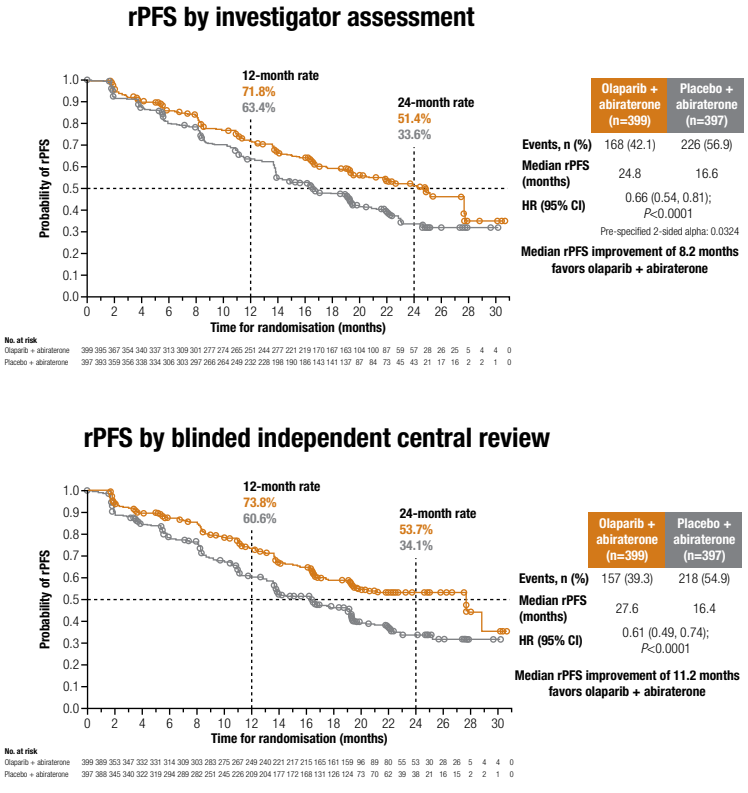


Figure 13. Radiographic progression-free survival (rPFS) in the PROpel trial in patients with metastatic castrate resistant prostate cancer treated with olaparib plus abiraterone compared with abiraterone alone[53]

MAGNITUDE study

The randomised, double-blind, placebo-controlled phase 3 MAGNITUDE study required patients with mCRPC to be screened for specific HRR biomarkers.[54] If they were HRR biomarker positive, patients were randomised to niraparib plus abiraterone plus prednisone (AAP) or placebo plus AAP as first-line therapy. If the patients were HRR biomarker negative, they were randomised in the same manner, but for an exploratory analysis only and the dose of niraparib was reduced to 200 mg to reduce the adverse events associated with higher dose of niraparib (**Figure 14**).[54] Overall, 53% of patients had *BRCA1/2* mutations.[54]

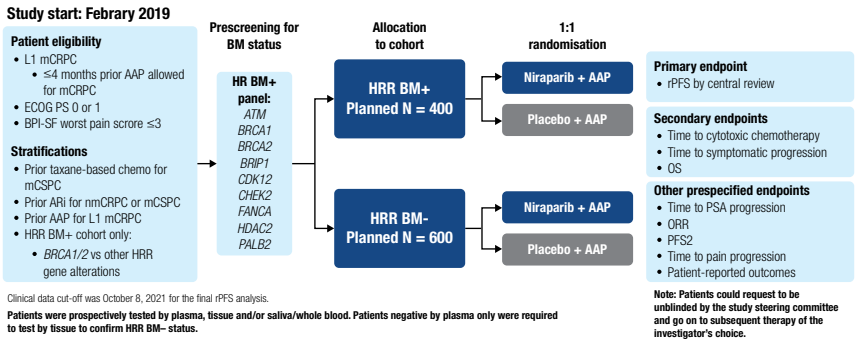


Figure 14. Study design of the MAGNITUDE study[54]

AAP = abiraterone plus prednisone; **BM** = biomarker; **BPI-SF** = Brief Pain Inventory-Short Form; **mCRCP** = metastatic castration-resistant prostate cancer; **mCSPC** = metastatic castrate-sensitive prostate cancer; **ECOG PS** = Eastern Cooperative Oncology Group performance status; **HRR** = homologous recombination repair; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **rPFS** = radiographic progression-free survival.

In patients with mCRPC without HRR biomarkers, there was no evidence of benefit with the addition of niraparib to AAP and this arm was dropped early after around 200 patients had been enrolled.[54] Niraparib plus AAP, compared with placebo plus AAP, significantly reduced the risk of rPFS (assessed by BICR) by 47% in patients with *BRCA* mutations (time to rPFS of 16.6 vs 10.9 months; HR 0.53; 95% CI 0.36, 0.79; p=0.0014) and by 27% in all HRR biomarker-positive patients (time to rPFS of 16.5 vs 13.7 months; HR 0.73; 95% CI 0.56, 0.96; p=0.0217). If abiraterone is introduced before starting the combination, the advantages of additional niraparib seemed to be lost. The adverse event profile was as expected, with 30% of patients reporting grade 3-4 anaemia and thrombocytopenia in 6.6% of patients treated with niraparib plus AAP.

Theranostics

Radionuclide treatment with lutetium-177-PSMA-617 has high response rates, low toxic effects, and reduces pain in men with mCRPC who have progressed after conventional treatments.[55]

In the TheraP trial, patients with mCRPC were administered lutetium-177-PSMA-617 every 6 weeks for up to six cycles or cabazitaxel every 3 weeks for up to ten cycles in the third-line setting.[56] This study showed that, in carefully selected patients based on PSMA-PET and 18F-fluorodeoxyglucose (FDG) imaging scans, lutetium-177-PSMA-617 compared with cabazitaxel led to a higher PSA response (66% vs 37%) and fewer grade 3 or 4 adverse events.

The randomised, open-label phase 3 VISION trial enrolled men (n=831) with PSMA-positive mCRPC based on PET/CT scan with ^{68}Ga-PSMA-11, and with no FDG imaging required.[34, 57] The men had previously been treated with at least one next-generation AR-signalling inhibitor and one to two taxane regimens.[34, 57] Men were randomised 2:1 to lutetium-177-PSMA plus SOC versus SOC alone. SOC was investigator determined but excluded cytotoxic chemotherapy and radium-223. Lutetium-177-PSMA plus SOC versus SOC alone improved OS (HR for death, 0.62; p<0.001) and rPFS (HR 0.40; p<0.001).[34, 57]

Bone health in mCRPC

The PEACE III study investigated if patients with mCRPC randomised to first-line treatment with enzalutamide alone versus enzalutamide plus radium-223 improved rPFS.[58] The study was prematurely unblinded because of a significant increase in the fracture rate in the combination abiraterone and radium-223 arm which led to the mandatory use of bone protecting agents (BPA) in the rest of the trial.[58] Prior to the mandatory use of BPA, 45% of patients were not receiving a bone targeted therapy. After 18 months without a BPA, the fracture rate was 45.9% with enzalutamide plus radium-223 and 21.9% with enzalutamide alone. Strikingly, in both arms, the risk of fracture was almost abolished by continuous administration of a BPA (4.3% and 2.6%, respectively) at 18 months.[58]

Conclusion

Professor Saad noted that historically treatment for patients with prostate cancer had been "simple but depressing." When treating mCRPC today, "things are a lot more complicated but so much better for patients," Professor Said concluded.

Q&A discussions

The PROpel study indicated a benefit of combined olaparib plus abiraterone therapy over abiraterone therapy alone in patients with and without DNA repair defects.[53] However, in the MAGNITUDE study, there was no benefit of adding niraparib to abiraterone plus prednisone in patients without DNA repair defects.[54] Is there an explanation for the different outcomes with the PARP inhibitors in these trials?

Professor Fred Saad It is hard for me to argue with strong data, although there are multiple differences between these trials. The MAGNITUDE trial (which was a relatively small study) suggested that when using niraparib in this combination in non-HRR mutated patients, the dosing is important, the timing is important, and the tolerability is important. If a patient had a HRR mutation, I would definitely treat them with either of these triple therapies, but I think continued research is needed to determine which patients without HRR mutations benefit the most from combinations involving PARP inhibitors.

Is M0 on conventional imaging the same staging as M1 on PSMA-PET?

Professor Louise Emmett: CT and bone scans are old technologies that rely on anatomy and changes in the bone, but changes start in the marrow before sclerotic changes occur. So I would say this staging on conventional compared with PSMA-PET is accurate, and is not upstaging. We need to incorporate new technologies (e.g., PSMA-PET), as well as conventional imaging, into all randomised trials.

In the nmCRPC studies, there was an increase in noncancer deaths. Why might this be occurring? Could it be due to interactions of the prostate cancer treatment with concomitant medications?

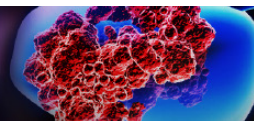
Professor Fred Saad: In patients with mHSPC who live long enough, 30% of the deaths are not due to prostate cancer - so we're keeping patients alive longer and we need to consider de-intensifying treatment in some patients who might not need life-long therapy.

Professor Lisa Horvath: It is important in patients who have mHSPC and are otherwise well, that we also conduct other age-appropriate screening investigations (e.g. a faecal occult blood test) for the presence of other cancers so that they can be treated appropriately.

Professor Jarad Martin: Patients with nmHSPC may be on novel agents for years. In these patients, an "oligo-progression phenomenon" may occur, with one metastasis that is increasing on PSMA-PET scanning, while all the rest of the prostate cancer appears to be under control. Stereotactic body radiotherapy may be used to control this metastasis.

I also want to highlight the DECREASE trial being conducted around Australia. In the new era of PSMA-PET, which is far more sensitive than conventional imaging, men with mCRPC who are M0 on conventional imaging may be M1 on PSMA-PET staging. The DECREASE study, which is being conducted in men with mCRPC, is investigating if darolutamide plus consolidation radiotherapy (stereotactic ablative body radiotherapy) to PSMA-detected sites of disease will improve the clinical outcomes compared with treatment with darolutamide alone. The primary outcome measure is undetectable PSA at 12 months.

Professor Fred Saad: If stereotactic ablative body radiotherapy can help to de-intensify therapy, it becomes an attractive option. In the hormone-sensitive metastatic setting, if we can target the lesion and avoid keeping patients on lifelong ADT, this would be a big advantage, especially in terms of quality of life for the patient.



How often should denosumab be administered to patients with mCRPC?

Professor Fred Saad: The current recommendation of use of denosumab comes from trials based on injections of denosumab once every 4 weeks in patients with HSPC. In Canada, we administer denosumab at this frequency, at least for the first or second year of treatment. If after a year or two of prostate cancer therapy, the patients are having a complete response and they are likely to live for a further 5 or 6 years, I would reduce the frequency of administration of denosumab to reduce the risk of osteonecrosis of the jaw (ONJ). In patients with mCRPC, who are not doing so well after two years, the decision to treat with denosumab is made case by case. I would rather start early with denosumab and pull back, than wait until it is too late.

Professor Lisa Horvath: The PEACE III study in men with CRPC showed that the risk of fractures was reduced when patients received bone-protecting agents,[58] with the risk of ONJ being less than 5%. The risk of ONJ can be reduced by patients visiting a dentist before denosumab is initiated, and then regularly throughout denosumab treatment. Once fractures start to occur in patients, it's a slippery slope in terms of their quality of life and disability.

For a patient with *de novo* mHSPC (enrolled in the UpFrontPSMA trial) treated with lutetium-PSMA, what is your experience of doing a channel TURP for urinary outflow obstruction?

Dr Renu Eapen: We don't generally give lutetium-PSMA for *de novo* mHSPC unless it is in a trial (e.g. the UpFrontPSMA[59]). The LuTectomy trial[60] is giving upfront lutetium-PSMA to men with high-risk localised/locoregional advanced prostate cancer followed by radical prostatectomy and pelvic lymph node dissection. What we found is that tissue planes are largely preserved, and we haven't really seen any increase in surgical difficulty. With transurethral resection of the prostate, we have less experience in those treated with lutetium-PSMA. However, extrapolating from the evidence from the LuTectomy trial, I would not anticipate any difficulty.

How do you know if you're under treating or over treating a nmCRPC patient? What indication do you look out for?

Professor Lisa Horvath: I think it's about looking at the criteria used for inclusion in the trials. It's really about the PSA doubling time. If your PSA doubling time is under 10 months irrespective of your PSMA-PET scan results, and the patient is well, then they can be treated with an androgen receptor signaling inhibitor, assuming it is well tolerated. You are probably over treating if their PSA doubling time is over 18 months**.**

Professor Fred Saad: In our guidelines in Canada, we include life expectancy when assessing the treatment plan for a patient. For a patient with a life expectancy of less than five years (such as those aged over 85 years), even if they are high-risk, nmCRPC, I would question whether we need to treat them aggressively. It is about personalising care. Anybody with a PSA doubling time beyond ten months, we do not treat.

Can you explain why very different selection criteria were used in the TheraP and VISION trials which were conducted in men with mCRPC?

Professor Louise Emmett: There were very specific reasons for the selection criteria that were chosen in each of these trials. I think we need to do a lot more work to know how to select patients for treatment based on PSMA-PET scans (almost no target versus a very intense target) and whether or not to use FDG PET scans in the long term.

Professor Fred Saad: The group of patients with CRPC is not homogeneous. However, for those that respond to lutetium-PSMA, I would like to see trials that investigate combination therapies.

Professor Louise Emmett: I agree, I think combination therapy is where we should be heading. In Australia, the ENZA-p trial[61] is investigating the efficacy and safety of adding lutetium-PSMA to enzalutamide in patients with mCRPC. In the long-term, I think lutetium-PSMA is going to fit within a combination therapy setting.

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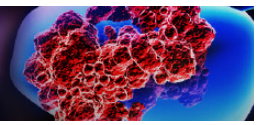

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