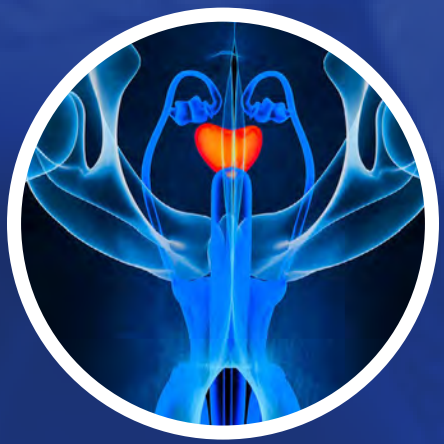
BENCH TO BEDSIDE
URO-ONCOLOGY
GU CANCERS TRIAD



Proceedings from the SIU B2B Uro-Oncology: GU Cancers Triad Virtual Meeting

November 11, 2022

Prostate Cancer

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mCRPC

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nmCRPC

XTANDI is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC). XTANDI has not been studied in patients with nmCRPC at low risk of developing metastatic disease. The benefit and risk profile in these patients is unknown.

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mCRPC=metastatic castration-resistant prostate cancer; mCSPC=metastatic castration- sensitive prostate cancer; nmCRPC=non-metastatic castration-resistant prostate cancer.

Reference: 1. XTANDI Product Monograph. Astellas Pharma Canada, Inc. January 24, 2022.

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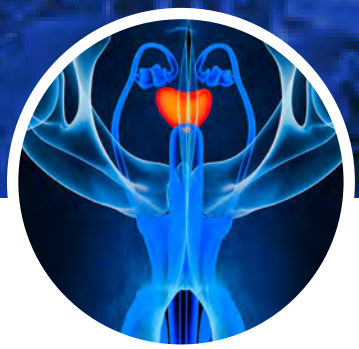

B2B: Prostate Cancer Summary

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The 4th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 42nd Annual Congress of the Société Internationale d'Urologie, was held on November 11th, 2022, at the Palais des congrès de Montréal in Canada, and transmitted live on the *SIU@U* virtual platform. The session on prostate cancer (PCa) was chaired by Dr. Derya Tilki (Germany). The first presentation in this session addressed the whos and hows of germline testing. This was followed by an update on artificial intelligence (AI)-derived predictive biomarkers and a presentation on management of pN1 disease. Next was a session on the use of prostate-specific membrane antigen (PSMA) theranostics to target PCa, followed by a session on challenges and progress in personalized therapy, starting with localized PCa and then moving on to metastatic disease.

The session opened with Dr. Elena Castro (Spain) discussing germline testing in PCa. She pointed out that about 60% of attributed risk for PCa is estimated to be due to genetic factors. Family history of PCa and other malignancies is a principal risk factor for the disease[1]. The prevalence of inherited mutations in genes associated with PCa among those with low-risk localized PCa is similar to that of the general population (about 3%). However, the prevalence of germline mutations increases among those with high-risk disease (about 6%) and is even higher in metastatic PCa (8% to 12%) [1–4]. Alterations are most frequently found in DNA repair genes, with *BRCA2* most commonly affected, even across different populations with different ethnic backgrounds[1,2,5,6].

Among patients with PCa undergoing active surveillance who carry germline *BRCA2* mutations, the probability of histologic upgrade is high, and about 50% will require treatment after 5 years of follow up[7]. Patients with localized disease who receive conventional treatment in the form of surgery or radiotherapy have an elevated chance of progressing to metastatic disease if they have *BRCA2* mutations[8]. Among those, patients who develop metastatic castration-resistant PCa (CRPC) progress more rapidly when treated with currently available therapies, excluding poly(ADP-ribose) polymerase (PARP) inhibitors, if they have *BRCA2* mutations[2]. The impact of germline mutations in other genes remains unknown.

The presence of germline *BRCA1/2* mutations can help predict response to treatment for PCa. These patients respond to PARP inhibitors, with no difference in response rate based on the presence of germline vs. somatic alterations[9,10]. Patients with germline mutations in mismatch repair (MMR) genes may respond to programmed cell death-1/programmed death-ligand 1 inhibitors, especially if they also have microsatellite instability[11]. Importantly, germline testing alone

may miss up to 50% of patients eligible for targeted therapies, highlighting the relevance of also conducting somatic testing. Nevertheless, germline testing remains a critical aspect of PCa management because germline mutations found in a patient may also be present in their relatives. These individuals may be candidates for early cancer prevention or detection programmes. Given their importance in guiding management decisions, both somatic and germline testing are now recommended in multiple clinical practice guidelines[12–14].

Characteristics of mutation carriers are yet to be identified. Age at diagnosis, prostate-specific antigen (PSA) level, histology, trend to metastatic disease, and trend to rapid progression are not strongly reliable indicators of the presence of germline mutations[1–3,15]. Currently, the best predictor of a germline mutation is family history, with up to 30% of carriers having a family history of cancer[1–3,15]. While intraductal histology has been associated with *BRCA2* alterations, Dr. Castro and her group found no difference in frequency between carriers and non-carriers of *BRCA2* alterations[16]. Nonetheless, an association was identified between this histology and biallelic *BRCA2* alterations, whether they were somatic or germline, likely because intraductal histology is associated with genomic instability[16].

A recommendation that arose from the 2019 Philadelphia Prostate Cancer Consensus Conference was that germline testing be performed in all patients with advanced disease, using broad panels that include *BRCA1*, *BRCA2*, MMR genes, *ATM*, *HOXB13*, *CHEK2*, *PALB2*, *BRIP1*, as these are the genes associated with PCa disposition[17]. Other genes can also be included if family history suggests another alteration may be present[17]. Patients with nonmetastatic disease should also undergo germline testing if they have Ashkenazi Jewish ancestry, advanced disease, grade group ≥ 4 disease, or intraductal/ductal pathology[17]. Unaffected men with a family history of PCa and other tumours that may suggest the presence of germline mutations should also be tested for mutations found in *BRCA1*, *BRCA2*, MMR, and genes implicated via family history[17]. The likelihood of these genes being germline is about 70%, according to research by Turnbull at al. (in prep).

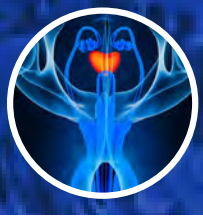
The European Society for Medical Oncology Precision Medicine Working Group recommends germline testing for variants that are predicted to result in a protein loss of function, as well as those that have been classified as pathogenic or likely pathogenic in publicly available databases with an allele frequency > 20%[18]. Those with a lower allele frequency are most likely somatic. Germline analysis should also be conducted when the germline conversion rate is > 10%[18]. In hypermutated tumours, the possibility of underlying germline MMR should be excluded[18].

Normal/negative tumour sequencing findings should not be interpreted to mean normal/negative germline results[18] because a substantial proportion of germline mutations are not detected through this approach[19]. Tumour profiling may miss germline mutations because acquired changes in the tumour can mask a mutation in the germline. Some tumour testing platforms may filter out germline variants to inform only somatic variants, and some assays may not analyze genes completely. In addition, some genes associated with cancer predisposition syndromes may not be included in tumour testing panels[20].

The likelihood of missing a germline mutation varies from gene to gene, ranging from 0% to 37%[19]. Tumour sequencing will identify most single nucleotide variants, but is more likely to miss deletions and duplications[19]. Results are also influenced by tumour sample quality and the presence of somatic copy number alterations, which is common in PCa[19]. In PCa specifically, tumour sequencing alone fails to detect about 7% of germline pathogenic variants[19]. Thus, patients who are at high risk of carrying germline mutations, such as those with a family history or with aggressive disease, should be offered germline testing despite negative tumour sequencing results.

An algorithm has been recently published to help guide clinicians in optimizing tumour and germline testing in patients with advanced PCa in the Canadian setting[21].

In summary, Dr. Castro recommended germline testing for PCa patients with metastatic/high-risk



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localized disease, as well as for those with a personal/family history that may suggest cancer predisposition (even in the event of negative tumour sequencing results). When in doubt, she said, patients should be referred for genetic counselling. During the Q&A, Dr. Castro explained that the cost of germline testing is reasonable and is becoming less expensive. Nevertheless, there is a paucity of genetic counsellors.

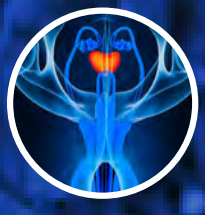
Next, Dr. Daniel E. Spratt (United States) provided an update on AI-derived predictive biomarkers for PCa. Prognostic biomarkers in patients diagnosed with PCa, he said, help estimate risk of recurrence and determine who requires more intensive treatment. Predictive biomarkers, on the other hand, help identify the relative impact of a given therapy. PCa continues to have a heavy reliance on Gleason score, PSA, digital rectal exam, and magnetic resonance imaging (MRI), all of which have significant limitations [14]. None of these were developed or trained with the intent of optimizing either prognostication or prediction of treatment response. In fact, it has been suggested that PSA, T-stage, Gleason grade, and the National Comprehensive Cancer Network® risk groups are barely better than chance for risk stratifying patients[22]. In addition, none of these are predictive of which patients would benefit from short- or long-term androgen deprivation therapy (ADT)[22]. Multiple candidate gene expression predictive biomarkers include PORTOS, ADT-RS, and AR-Activity, but none of these have been consistently and rigorously validated for routine clinical use.

Dr. Spratt emphasized that what is needed are objective, quantitative biomarkers that can reliably offer prognostic or predictive information. AI has the potential to use both human-interpretable and non–human-interpretable features of digital histopathology images to offer predictive information. Many companies are now attempting to use AI technology to predict Gleason grade, but since Gleason grade itself is not highly prognostic, this is unlikely to improve prognostic or predictive ability in clinical practice. A more useful goal is for the AI technology to directly prognosticate outcomes or predict response to individual therapies.

Dr. Spratt and colleagues collaborated with NRG Oncology using data from five large phase 3 trials of radiotherapy and/or ADT for the treatment of PCa. In total, there were data from 5564 patients, including 16 204 pathology slides and 16 TB of imaging data to develop a predictive biomarker. Using 4 of these trials (n = 3935), the investigators used AI to develop the ArteraAI-Predict ADT biomarker, which uses patient, clinical, and digital pathology imagery features to predict response to ADT vs. radiotherapy alone[23]. They then validated their findings using the NRG/RTOG 9408 cohort, a trial of 2028 PCa patients who were randomized to short-term ADT plus radiotherapy or radiotherapy alone. In this trial, 55% of patients were classified as intermediate risk. In this validation cohort (n = 1719), the multi-modal, deep learning ArteraAI-Predict ADT biomarker predicted that 63% of men would not benefit from ADT, whereas 37% would. The predictive model was primarily driven by features present in the digital pathology images, with lesser contributions from PSA, T-stage, and grading. The patients who were positive for the ArteraAI-Predict ADT biomarker had a substantial reduction in distant metastasis at 15 years with the addition of ADT to their treatment (HR [hazard ratio] = 0.33; 95% confidence interval [CI] 0.19 to 0.57). Among those who were biomarker negative, ADT added no benefit (HR = 1.00; 95% CI 0.63 to 1.56), with an interaction $P = 0.002$[24].

Based on these findings, Dr. Spratt estimated that approximately two-thirds of the men with PCa for whom ADT is recommended could safely avoid this treatment, regardless of their prognosis, due to the lack of absolute benefit. Nevertheless, during a Q&A, he stated that more research should always be encouraged to refine and optimize biomarkers for widespread use, especially for predictive biomarkers such as ArteraAI-Predict ADT. In time, Dr. Spratt and his group hope to validate this work in another large phase 3 trial. Lastly, there is a lack of historical precedent on how the United States Food and Drug Administration (FDA) and other regulatory agencies can adapt rapidly to AI-driven biomarkers whose model can change with more data.

In the subsequent presentation, Dr. Derya Tilki (Germany) discussed management of pN1 PCa, a



condition that she noted is being diagnosed with increasing frequency[25]. While a randomized trial demonstrated higher overall survival (OS) among patients with pN1 PCa who received immediate vs. delayed ADT[26], suggesting that the presence of lymph node metastases is a sign of widespread disease, recent observational studies suggest that not all pN1 patients have systemic disease[27,28]. Thus, some men may be overtreated with immediate and lifelong ADT, highlighting a pressing need for better individualization of therapy.

Indeed, in a study of 209 pN1 patients with 1 or 2 histologically proven positive lymph nodes who did not receive adjuvant treatment, 27% were free of biochemical recurrence (BCR) after 5 to 10 years[29]. Similarly, another study has demonstrated that 28% of patients with pN1 disease remained free from BCR at 10 years. In addition, an increased risk of BCR was observed among patients with higher Gleason scores and 3 or more positive nodes[27].

Currently, only retrospective data are available regarding the addition of adjuvant radiation to ADT in pN1 disease. It has been demonstrated that this treatment approach leads to improved cancer-specific survival (CSS)[30], as well as improved OS compared to ADT alone (HR = 0.46) or observation (HR = 0.41)[31]. In a study by Dr. Tilki's group, adjuvant radiotherapy was associated with a significant reduction in all-cause mortality risk, compared with early salvage radiation, regardless of the number of involved lymph nodes. The magnitude of the effect of adjuvant radiation increased by 8% with each additional positive lymph node, and those with ≥ 4 positive nodes derived the greatest benefit from adjuvant treatment[32].

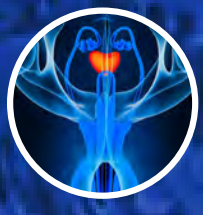
Retrospective data are also equivocal regarding the addition of ADT to adjuvant radiotherapy in pN1 disease. A single-centre analysis by Bravi et al. found no OS benefit with the addition of ADT to radiotherapy[33]. Conversely, Wong et al. demonstrated better outcomes with the addition of ADT[34]. More recently, in the controlled RADICALS-HD trial, patients who received postoperative radiotherapy, either immediately or as salvage, were randomized to radiotherapy alone, radiotherapy plus 6 months of ADT, or radiotherapy plus 2 years of ADT. Those who received long-term ADT had improved metastasis-free survival (MFS) compared to those who received short-term ADT or no ADT at all. No benefits were observed between the no-ADT and short-term ADT groups[35].

The benefits of chemotherapy in this setting also remain equivocal. In the SPCG-12 study, 459 high-risk PCa patients, 12% with pN1 disease, were randomized to 6 cycles of adjuvant docetaxel or surveillance. After a median follow-up of 56.8 months, there was no difference between the 2 groups with respect to disease-free survival (DFS), defined as a rising PSA > 0.5 ng/mL[36]. Dr. Tilki noted that these findings may be influenced by the failure to combine docetaxel with ADT and the inclusion of patients not classically considered to be at very high risk for relapse (eg, those with pT2, Gleason 7 tumours).

There are several upcoming studies in this space. In the DASL-HiCaP (ANZUP 1801) trial, patients with very high-risk PCa, including patients with pN1 disease, are being randomized to receive either darolutamide or placebo in addition to ADT and radiation in the first-line or salvage setting[37]. The NRG-GU008 (INNOVATE) study is looking specifically at pN1 disease after prostatectomy. Patients are stratified by PSA status (undetectable or rising after previously being undetectable) and randomized to radiotherapy plus ADT, with or without the addition of apalutamide, for 2 years[38].

A systematic review of management of patients with node-positive PCa at radical prostatectomy and pelvic lymph node dissection has been recently conducted[39]. The review comprised 26 studies, including 12 357 patients, most of whom presented with pN1 disease and experienced BCR after surgery. Long-term DFS was reported in selected patients. The use of adjuvant radiotherapy, with or without ADT, was shown to improve survival in men presenting with locally advanced disease and a higher number of positive lymph nodes. Risk stratification according to pathological Gleason score, number of positive nodes, and pathological stage is key for selection of the optimal postoperative therapy[39].

The uncertainty regarding the optimal management of pN1 disease is reflected in the European Association



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of Urology guidelines. Treatment options, including the addition of adjuvant ADT with or without radiotherapy, all have weak recommendations[14].

In a Q&A, Dr. Tilki specified that the decision to add abiraterone to ADT and radiotherapy in patients with pN1 disease following prostatectomy, based on the STAMPEDE trial[40], which was conducted in patients with intact prostates, requires the extrapolation of information on clinically node positive disease to pathologically node positive disease. This question is presently under investigation in several trials.

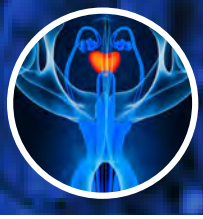
Next, Dr. Andrew L. Laccetti (United States) discussed PSMA theranostics to target PCa. PSMA is a transmembrane glutamyl carboxypeptidase that is heavily conserved in > 80% of PCa, regardless of disease state or distribution. Its expression is consistent through hormonal therapy, with some data suggesting expression increases as androgen receptor (AR) signalling declines[41–43]. PSMA is higher in PCa, with limited expression in healthy native tissue, but there is some expression endovascularly in some non-prostate malignancies and in some normal tissue, such as the salivary glands[41–43].

For these reasons, PSMA has emerged as an attractive target for novel PCa therapies, including theranostics, a novel strategy that combines molecular-based imaging with treatment strategies that leverage targeted small molecules with radionucleotides[41,44]. Tools such as the gallium-68 (^{68}Ga) PSMA positron emission tomography (PET) or piflufolastat fluorine-18 (^{18}F) PSMA PET are used to identify and localize expression of PSMA on prostate tumours. These may then be matched to therapeutic forms of PET tracers that are tethered to radioactive payloads, such as lutetium-177 (^{177}Lu) or actinium-225 (^{225}Ac), to deliver targeted radiation[41,44].

^{177}Lu-PSMA-617 targeted radioligand therapy (Lu-PSMA) is the best studied PSMA-directed radiotheranostic to date. It comprises the small molecule PSMA-617, which targets PSMA and is linked to the beta emitter ^{177}Lu. After injection, Lu-PSMA is endocytosed via the PSMA receptor, delivering the radioactive payload intracellularly, which creates cytotoxic effects via double-stranded DNA breaks[45].

Lu-PSMA was recently approved by the FDA as the first PSMA-directed radiotheranostic based on the results of the phase 3 VISION trial. Men with heavily pretreated metastatic CRPC were randomized to receive 4 to 6 cycles of Lu-PSMA combined with standard of care or standard of care alone, consisting primarily of oral AR pathway inhibitors (ARPI) or ADT monotherapy. Excluded from standard of care were chemotherapy, radium-223, immunotherapy (IO), and targeted therapies. All patients had previously received ≥ 1 oral ARPI and taxane chemotherapy, and all had a positive ^{68}Ga-PSMA PET. In this trial, Lu-PSMA therapy was associated with a 38% reduction in risk of death and about a 4-month improvement in median OS. Also improved were radiographic progression-free survival (rPFS) and time to symptomatic skeletal-related events[46]. Finally, Lu-PSMA treatment was also associated with improved quality of life and reduced pain[47]. Benefits in rPFS and OS were observed regardless of administration of concurrent ARPI therapy. There was a suggestion that the addition of second-generation ARPI improved outcomes, but the VISION trial was not powered to detect this[48].

Despite these observed benefits, 54% of patients did not respond to Lu-PSMA; non-response was defined as a decline in PSA ≥ 50%. In addition, 48% of patients did not achieve an objective response[49]. As a result, an active area of investigation is to develop strategies to identify responders. In a retrospective analysis of phase 2, single-arm Lu-PSMA study data combined with data collected from compassionate use experience, investigators developed a nomogram to predict responders based on such factors as chemotherapy exposure, hemoglobin level, time from diagnosis, and tumour distribution features. They observed that increasing values in the nomogram corresponded to a reduced probability for survival at 12 and 18 months. In validating this nomogram, they created high-risk and low-risk groups who had substantially different median OS and PSA–progression-free survival (PFS) outcomes following administration of Lu-PSMA[50]. This prognostic marker has not been evaluated prospectively and is not currently considered a predictive marker. Nevertheless, there are plans to include this marker in future prospective studies.



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Another biomarker under development is the signal intensity on PSMA PET scan. In a retrospective analysis of the TheraP/ANZUP 1603 trial, investigators established a median PSMA standardized uptake value (SUV) of 10.0 as a cutoff, which corresponded to a response rate of 91% PSA decline ≥ 50% from baseline (odds ratio for response = 12.2, $P = 0.03$)[51].

In order to develop strategies for improved response to Lu-PSMA, it is important to understand mechanisms of resistance in PCa. There is prospective evidence that suboptimal radiation dose may be an underlying mechanism[52]. In addition, genetic studies in animal models suggest mutations in the oxidative stress pathway, notably loss of *TP53*, may be involved in mechanisms of resistance[53].

Proposed strategies for improving response to PCa theranostics include combining PSMA-PET with fluorodeoxyglucose (FDG)-PET to exclude non-PSMA expressing tumour sites, determining optimal PSMA expression thresholds, optimizing dosimetry, and employing genomic profiling[54]. Multiple ongoing trials are exploring the combination of theranostics with PARP inhibitors (which are known to increase DNA damage) and IO as well as ARPIs (which increase expression of PSMA). Finally, there is a need to determine the optimal ratio of radioactive alpha/beta payload delivery.

Ongoing trials involving Lu-PSMA are now focusing on moving the treatment to earlier in the disease course. There are several clinical trials evaluating Lu-PSMA in the metastatic CRPC setting using it prior to chemotherapy. One of these trials is the phase 3 PSMAfore, in which patients are randomized to Lu-PSMA or a change in ARPI[45]. The SPLASH trial has a similar design, but it compares Lu-PSMA with abiraterone or enzalutamide[55]. In ENZA-p, patients are randomized to Lu-PSMA with enzalutamide or enzalutamide alone[56]. The PRINCE trial is exploring the combination of Lu-PSMA with pembrolizumab in metastatic CRPC. The underlying hypothesis of this study is that the theranostic will result in increased neoantigen exposure, which may synergize with pembrolizumab to promote a response[57].

In the setting of metastatic castration-sensitive PCa (CSPC), the PSMAddition trial is randomizing treatment-naïve patients to Lu-PSMA with standard of care or standard of care alone. In this trial, standard of care is defined as ADT with an oral ARPI[58]. The UpFrontPSMA trial has a similar design, except standard of care is defined as docetaxel. The trial is also utilizing FDG-PET and PSMA-PET for trial inclusion[59]. Ongoing clinical trials are examining use of Lu-PSMA in combination with PARP inhibitors, oral anti-androgens, and IO.

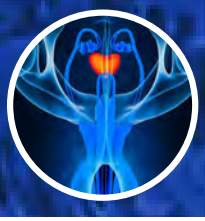
Non-PSMA targets for theranostics are also being evaluated in PCa. Six-transmembrane epithelial antigen of prostate (STEAP) 1 is a highly conserved transmembrane protein in metastatic CRPC. It is currently under active development as a bispecific antibody[60]. There has been some investigation into development of PSMA tracers for STEAP1 in addition to theranostics[61].

Human kallikrein-2 (HK2) is a well-conserved protein in healthy prostate tissue as well as PCa. It is in phase 1 testing using a theranostic incorporating ^{225}Ac[62]. The expression of HK2 is AR mediated. Therefore, there is a feedback synergy with this approach whereby DNA damage increases AR signalling, which in turn increases HK2 expression, theoretically increasing uptake of the theranostic[62–64].

Finally, delta-like ligand 3 (DLL3), originally discovered as a small cell lung cancer marker, is also well-conserved in neuroendocrine differentiation of PCa, which is highly treatment refractory[65]. PET targeting and radiotheranostics are currently under development for DLL3[65].

During a Q&A, Dr. Laccetti explained that FDA approval of Lu-PSMA is limited to heavily pretreated patients with metastatic CRPC. In his practice, he uses it as the standard of care in these patients. Nevertheless, there is a high demand in the United States, which can make access to Lu-PSMA difficult. He is currently enrolling patients on clinical trials that include treatment with Lu-PSMA in earlier disease settings.

The next presentation was by Dr. Martin E. Gleave (Canada), who discussed challenges in personalized therapy in the setting of localized disease, with a focus



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on neoadjuvant strategies. He noted there are several molecular prognostic biomarkers in use for localized PCa. While these can be useful for risk stratification, particularly for clinical trials, they are not yet helpful at guiding treatment decisions[66,67].

Neoadjuvant studies in localized PCa aim to improve outcomes, study mechanisms of response and resistance, and support drug development. Previous failed attempts to improve outcomes with neoadjuvant ADT did not select patients for high risk, were underpowered, and had inadequate endpoints to evaluate efficacy[68,69]. Low pathological complete response (pCR) rates persisted despite treatment intensification[68,69]. Questions remain as to how to evaluate pathological response as a surrogate of treatment benefit.

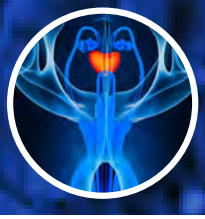
Based on evidence of benefits in advanced disease, investigators have evaluated the benefits of neoadjuvant doublet or triplet ARPI therapy in localized PCa, but findings have been disappointing. While depth of response has been shown to improve, pCR does not increase above 8%[70,71]. The ongoing phase 3 PROTEUS trial is investigating 6 months of neoadjuvant plus 6 months of adjuvant luteinizing hormone-releasing hormone analogue with or without apalutamide in men with high-risk localized PCa. The primary outcome is MFS, but pCR is also being used as a surrogate of efficacy[72].

Again spurred by positive trials in advanced disease, the combination of docetaxel plus ADT has been evaluated in localized PCa. An early Canadian study demonstrated feasibility and reasonable depth of response[73], which led to the phase 3 CALGB 90203 Alliance trial. A total of 750 patients with early high-risk PCa were randomized to neoadjuvant docetaxel plus prednisone and ADT, followed by radical prostatectomy, or radical prostatectomy alone. The primary endpoint was 3-year PSA recurrence, which was not different between the groups, but about 40% of patients received salvage radiation, ADT, or both prior to meeting the primary endpoint, which makes interpretation of the findings difficult. Actuarial PSA recurrence rates over time favoured the neoadjuvant therapy arm, as did freedom from treatment failure. OS data remain immature[74].

Genomic studies of a subset of biopsies obtained from the CALGB 90203 Alliance trial used tumour DNA content as an estimate of residual cancer burden. In the neoadjuvant group, there was a significant reduction in tumour DNA content[75]. When sequence tumour fraction was undetectable, PSA recurrence rates were lower[75]. This research is ongoing, with analysis of the DNA before and after treatment in the entire CALGB 90203 study population. So far, mutation frequencies of *TP53* have been shown to be higher in the post-treatment tissue, which may represent a treatment resistant population[75]. Conversely, the mutation frequency of *SPOP*, which correlates with sensitivity to ADT, was reduced in the post-treatment specimen[75]. Expression profiling has revealed a downregulation of AR target genes and upregulation of certain plasticity and neuroendocrine genes, which may reflect a role in resistance and survival in response to treatment stress[75].

In the metastatic setting, certain genetic alterations have been shown to influence response to specific systemic therapies[76–78]. This information, which is also rapidly emerging in the localized PCa setting, provides the opportunity for precision medicine. Several umbrella trials are already underway that are built on knowledge of the effect of specific mutations in PCa[11,46,79].

Genomic sequencing allows for matching of targeted agents to distinct genetic alterations, but these defects occur in a small proportion of patients[80], which hampers clinical testing in multiple single-agent, single-arm, phase 2 studies. The currently accruing GUNS trial was designed to address this gap. Tumour tissue in patients with high-risk localized PCa undergoes genetic sequencing and the patients receive combination treatments that target their genomic vulnerabilities. If a pCR > 8% is observed in the first 23 patients in a given treatment arm, this will be interpreted as a signal that the treatment is active, and the treatment arm will then be expanded. Arms that do not reach this threshold are discontinued. During a Q&A, Dr. Gleave specified that decisions regarding duration of neoadjuvant therapy in the GUNS trial are based on pragmatic and empiric factors. He also clarified that patients undergo both germline and somatic testing.



A challenge for the future, he said, will be to learn how to better evaluate the depth of response.

The last presentation in the PCa session was by Dr. Himisha Beltran (United States) who discussed current challenges and progress in personalized medicine for metastatic PCa. Genomic sequencing has rapidly advanced precision medicine in this setting, she said, but challenges remain, notably to identify somatic alterations associated with long-term response to systemic therapy, to identify and bring in non-genomic biomarkers that also influence treatment response, and to identify and combat emerging mechanisms of resistance.

Precision medicine incorporates the molecular findings of a patient's tumour to develop biomarker-driven approaches[81]. This has been challenged in the past by access to appropriate clinical assays and drugs, but has changed with a broad array of tumour and circulating tumour DNA (ctDNA) commercial genomic sequencing assays available and umbrella and basket trials that are starting to overcome some of these barriers. Another barrier is the cost of sequencing, particularly sequential testing, which is not always reimbursed. Finally, treatment resistance may be associated with loss of tumour suppressors and other molecular alterations that are often not targetable.

In the setting of metastatic CRPC, genomic alterations that are currently being targeted are usually focused on DNA repair, with homologous recombination relevant to PARP inhibitor use and MMR relevant to IO. While not genomic, PSMA is another biomarker routinely used in the clinic with PSMA PET/CT scans being used to select patients for Lu-PSMA-617. Other potential biomarker-driven approaches are still in development[76].

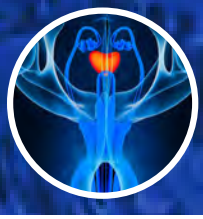
In the PROfound trial, over 4000 patients were screened in order to enroll 387 patients, most often using their untreated archival primary tumour tissue, suggesting that DNA repair gene alterations, at least those involving homologous recombination repair, are often early clonal events. Thus, repeat sequencing may not be necessary to identify candidates for PARP inhibitors. Nevertheless, > 30% of patients in this trial had screen failures due to the quality of the tissue, thus highlighting the need for biopsy or other assays such as ctDNA in certain cases[82]. Dr. Beltran highlighted that we are still learning which patients may benefit from PARP inhibitors. In PROfound, several of the gene mutations required for eligibility were either not identified or were underrepresented compared to anticipated rates.

At the Advanced Prostate Cancer Consensus Conference (APCCC) 2021 meeting, 96% of panelists recommended tumour genomic profiling for patients with metastatic PCa, usually at the time of diagnosis of any metastatic disease. Almost all recommended using the most recent archival tumour specimen or a new biopsy for genomic testing. Notably, 88% favoured tumour-based testing over liquid biopsy/ctDNA[83]. There is a high concordance between ctDNA and tumour tissue testing for DNA repair aberrations, but current ctDNA clinical assays do not report copy number aberrations including *BRCA2* homozygous deletion. There is also a risk of identifying clonal hematopoiesis alterations with ctDNA, which are mutations in normal white blood cells that can involve DNA repair genes that can lead to false positives[84].

Most panels that test for DNA repair aberrations find other alterations as well. *RB1* loss is one of the worst prognostic features in metastatic PCa[85,86]. While there are no drugs to target *RB1* loss, these patients may benefit from a more aggressive treatment approach, for example with early docetaxel.

AR mutations, splice variants, and amplifications are common in CRPC, and a number of studies have demonstrated their prognostic value[87–89]. While these are not currently considered actionable, work is ongoing into use of alterative approaches to target the AR, such as proteolysis-targeting chimera degraders to selectively target and degrade the AR via the ubiquitin-proteasome system. ARV-110 is an oral agent that targets both wild type AR and certain AR mutations, and has shown activity in AR-mutated PCa, with a pivotal trial planned for this population[90].

Dr. Beltran's team has been working with the US National Cancer Institute on a natural history study to try to better understand the "long tail" of mutations



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in PCa, that is, the large number of rare mutations, occurring in < 5% of patients[80].

Comparing whole exome sequencing of tissue biopsies with ctDNA findings can be used to identify clonal tumours, in which findings from ctDNA look almost identical to a single-site biopsy. However, tumours with subclonal differences detected on ctDNA may not be detected via single-site biopsy. These subclonal differences are often ignored, but may evolve to contribute to treatment resistance and even become more clonal[91].

It is important to recognize that genomics is only one part of how cancer evolves and responds to treatment[49]. A subset of patients lose PSMA expression and are therefore not eligible for Lu-PSMA-617. Even among those who remain PSMA-positive, there is considerable heterogeneity in response to Lu-PSMA[92–94].

Many biomarkers in PCa have been discovered by going from genotype to phenotype, but much can also be learned by going from phenotype to genotype, especially with respect to identifying rare, exceptional responders as well as extreme resistance phenotypes. One of these is the small cell/neuroendocrine phenotype, which represents a very aggressive form of PCa that is typically treatment emergent and often behaves much like small cell lung cancer, with visceral metastases and low PSA progression. These patients often lose PSMA expression, in part due to loss of AR expression and signalling[95]. Neuroendocrine transformation should be suspected in patients with these features[96]. Current understanding of these tumours is evolving. For now, treatment is focused on use of therapies traditionally used for small cell lung cancer[95]. Guidelines do not address when to re-biopsy to look for neuroendocrine transformation. Dr. Beltran considers re-biopsy for patients with very aggressive disease, low PSA, PSMA negativity on PET scanning, visceral metastases, or history of mixed or variant histology.

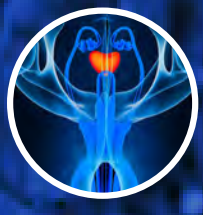
Research by Dr. Beltran and colleagues has revealed that neuroendocrine tumours arise clonally from prostate adenocarcinoma, are enriched with *RB1* and *TP53* loss, and are characterized by epigenetic reprogramming[95]. Epigenetics drive changes in phenotype in the context of the same genotype[97]. Some of these changes are driven by DNA methylation, which is not typically evaluated in the clinic but could be leveraged to identify neuroendocrine disease[95]. Many of these epigenetic changes drive transcriptional changes, suggesting that transcriptomics could represent another approach to identifying subsets of advanced PCa[91]. Dr. Beltran is working on the development of a phase 2 Alliance umbrella trial that incorporates transcriptomic profiling. She and her team have already identified some therapeutic targets based on the identification of transcriptional changes.

DLL3 is a cell surface marker that is overexpressed in neuroendocrine PCa and is acquired with treatment resistance[98]. There may be opportunities for imaging[65] and targeting DLL3. Dr. Beltran and her team have been working on a T-cell engager that targets DLL3, binding it on tumour cells as well as binding immune cells, thus bringing those immune cells into the tumour microenvironment. This approach has been successful in preclinical models of neuroendocrine PCa in research that is currently unpublished.

Future efforts in the area of precision medicine will focus on continued development and validation of biomarkers that help predict which patients will respond to specific therapies. Another focus is the identification of new targets, which requires looking beyond genomics. Novel biomarkers will require rigorous development, quantification, and validation.

When using a precision medicine approach, she concluded, patient factors, tumour factors, assay factors, and drug access considerations all play important roles. Multiple barriers still exist, and these will require collaborative efforts to be overcome.

During the Q&A, Dr. Beltran reported that she conducts fewer repeat solid tissue biopsies in the metastatic setting than she did before. Instead, she uses archival tissue sampling for patients with CSPC and ctDNA for patients with CRPC. Metastatic biopsies are usually reserved for patients in whom she suspects small cell or very aggressive disease. How to optimize sequential biopsy testing is an important question still unanswered.



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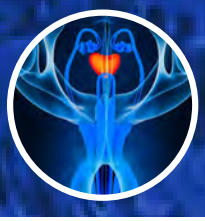
Abbreviations used in the text

Ac	actinium
ADT	androgen deprivation therapy
AI	artificial intelligence
APCCC	Advanced Prostate Cancer Consensus Conference
AR	androgen receptor
ARPI	androgen receptor pathway inhibitor
BCR	biochemical recurrence
CI	confidence interval
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
CSS	cancer-specific survival
ctDNA	circulating tumour DNA
DFS	disease-free survival
DLL3	delta-like ligand 3
F	fluorine
FDA	United States Food and Drug Administration
FDG	fluorodeoxyglucose
Ga	gallium
HK2	human kallikrein-2
HR	hazard ratio
IO	immunotherapy
Lu	lutetium
Lu-PSMA	^{177}Lu-PSMA-617 targeted radioligand therapy
MFS	metastasis-free survival
MMR	mismatch repair
MRI	magnetic resonance imaging
OS	overall survival
PARP	poly(ADP-ribose) polymerase
PCa	prostate cancer
pCR	pathological complete response
PET	positron emission tomography
PFS	progression-free survival
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
rPFS	radiographic progression-free survival
STEAP	six-transmembrane epithelial antigen of prostate
SUV	standardized uptake value



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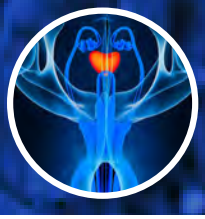

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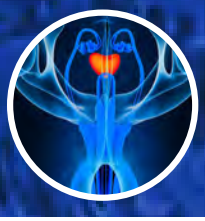

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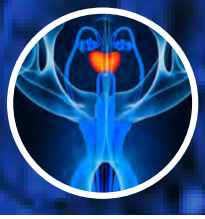

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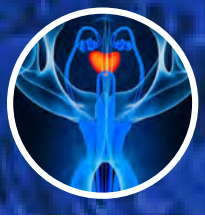

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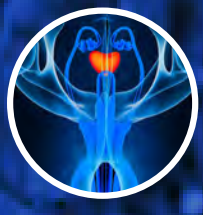

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