Review

Prostate Cancer Foundation Hormone-Sensitive Prostate Cancer Biomarker Working Group Meeting Summary

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Androgen deprivation therapy remains the backbone therapy for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC). In recent years, several treatments, including docetaxel, abiraterone + prednisone, enzalutamide, and apalutamide, have each been shown to demonstrate survival benefit when used upfront along with androgen deprivation therapy. However, treatment selection for an individual patient remains a challenge. There is no high level clinical evidence for treatment selection among these choices based on biological drivers of clinical disease. In August 2020, the Prostate Cancer Foundation convened a working group to meet and discuss biomarkers for hormone-sensitive prostate cancer, the proceedings of which are summarized here. This meeting covered the state of clinical and biological evidence for systemic therapies in the mHSPC space, with emphasis on charting a course for the generation, interrogation, and clinical implementation of biomarkers for treatment selection. UROLOGY 00: 1–7, 2020. © 2020 Elsevier Inc.

Although the incidence of prostate cancer has stabilized or decreased in most age groups, the incidence of metastatic disease has increased among men 50-69 years of age while the incidence of fatal prostate cancer has remained unchanged in men under 55 years of age.[1,2] The results of recent clinical trials including CHAARTED, STAMPEDE, ENZAMET, LATITUDE, TITAN, ARCHES, and GETUG have offered several first-line combination treatment options with androgen deprivation therapy (ADT) in men presenting with metastatic hormone sensitive prostate cancer (mHSPC).[3-9] While they have also elucidated several prognostic clinical features, the optimal sequence in which to administer them and the potential of triplet therapy to further improve outcomes has not been determined in a robust fashion. In August 2020, the Prostate Cancer Foundation convened a working group to determine whether biomarkers would be of value in this population and, if so, to begin the work of identifying and validating these biomarkers (Fig. 1).

This review article summarizes the work presented and discussed at the first meeting of the Prostate Cancer Foundation Biomarker Working Group with the hope that sharing this information will engage the broader prostate cancer research community in our effort to identify and validate clinically meaningful biomarkers that improve the treatment of men presenting with mHSPC.

TERMINOLOGY

In the course of the meeting, the terminology used to describe the clinical states of prostate cancer emerged as a major point of discussion. Several terms have been used to describe the same clinical states. Among the most commonly used terms are castration-sensitive prostate cancer / castration-resistant prostate cancer (CSPC/CRPC) and hormone-sensitive prostate cancer / hormone-resistant prostate cancer (HSPC/HRPC). Each of these have specific caveats related to biologic and clinical accuracy as well as patient and caregiver perceptions and stigma. With the increasing potency of hormonal therapies, it will be worthwhile revisiting the nomenclature used in the description of distinct clinical states along the prostate cancer continuum. One possibility discussed is to use testicular androgen deprivation naïve for ADT-naïve disease, testicular androgen deprivation resistant for disease

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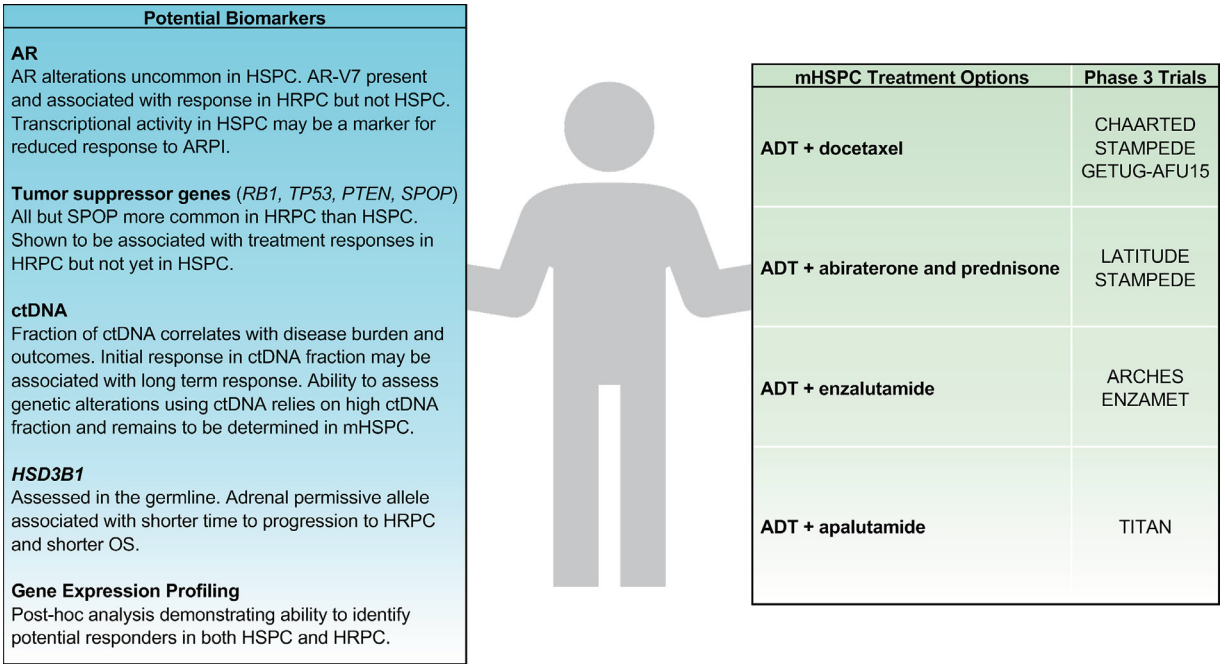

Figure 1. Potential biomarkers and treatment options based on reported trials for mHSPC.

progressing on ADT and complete androgen deprivation resistant for disease resistant to ADT + abiraterone, enzalutamide, or apalutamide. For the purpose of this summary the general consensus was that we use HSPC (as opposed to CSPC) for patients not treated with hormonal therapy and HRPC (as opposed to CRPC) for those patients who progress despite treatment with ADT. We acknowledge that these terms are inherently imperfect and there are common circumstances in which these terms may require clarification, especially in discussion with patients, and suggest that this topic be explored further in the future.

THE TREATMENT LANDSCAPE OF mHSPC

Maha Hussain reviewed the evolving treatment landscape of mHSPC as well as prognostic factors gleaned from and used in the trials that may serve as benchmarks for biomarker development.

Since Huggins and Hodges introduced the concept of androgen dependence in prostate cancer, the primary avenue of systemic therapy has been gonadal suppression or castration.[10] Androgen pathway targeting has dominated drug development and there are now several discrete pathways and targets. Early studies evaluated surgical vs medical castration, gonadal suppression vs peripheral blockade, LHRH-agonists vs antagonists, chemohormonal therapy, ADT with an antiandrogen, ADT with targeted bone therapy, and intermittent vs continuous ADT.

Recent trials have demonstrated a benefit to therapy intensification in mHSPC with chemohormonal therapy, ADT + abiraterone and prednisone, ADT + enzalutamide, and ADT + apalutamide.[3-9]

From these existing trials, one of the first prognostic factors that emerged was the location and number of metastases. Differences in overall survival are seen between patients based on the extent of disease as defined by location and number of metastases. This was demonstrated in earlier studies evaluating the use of ADT + nonsteroidal antiandrogens[11,12] and has been confirmed with contemporary trials.[13]

Another prognostic factor that has been identified is early nadir PSA as it reflects sensitivity of the disease to androgen deprivation alone. In the SWOG 9346 study on intermittent vs continuous ADT, the nadir PSA after 7-months from starting ADT was used to select for responders who would be eligible for randomization to intermittent vs continuous therapy.[14] The data demonstrate a role for nadir PSA as an intermediate biomarker predicting outcomes for early responders vs suboptimal or non-responders. This was confirmed in the CHAARTED and LATITUDE trials and supports the use of an early nadir PSA as an intermediate endpoint that may be helpful in screening therapeutic agents.[15-17]

Emerging areas in the development of new therapeutic strategies include the role of prostate therapy in the context of low tumor burden and management of oligometastatic disease with targeted therapy. Within the low burden of disease group, STAMPEDE has shown us that there is a potential role for primary tumor therapy,[18] while studies in metastasis-directed therapy (MDT) are ongoing such as MetaCURE which includes systemic therapy, stereotactic body radiation therapy (SBRT) to visible osseous lesions and aggressive radical prostatectomy (NCT03436654).[19] Questions that remain to be answered in the management of oligometastatic disease include the number and location of lesions which may benefit from MDT, the sensitivity and accuracy of imaging, as well as the objective of MDT (improvement in OS vs delay in use of systemic therapy).

With regard to molecularly-targeted therapy, the relative genetic complexity of metastatic hormone-resistant prostate cancer (mHRPC) and lesser genomic complexity of mHSPC would suggest that we may have better success in developing targeted therapies within mHSPC.[20]

In summary, Dr. Hussain reviewed the evolution of prostate cancer treatment with recent trials establishing a benefit to early therapy intensification, the improvement in overall survival among men presenting with mHSPC, narrowing of the racial gap for patients enrolled in clinical trials,[21] and prognostic factors demonstrated in these trials. How we currently choose initial therapy in these men is based partly on these factors but also based on toxicity, therapy duration, and physical and financial costs. A robust biomarker may not only be helpful to determine the appropriate first line treatment but may also be helpful in identifying patients who may benefit from less intensive therapy up front and in whom and when therapy deintensification could be considered.[22]

ANDROGEN RECEPTOR ALTERATIONS IN PROSTATE CANCER

Scott Dehm provided an overview of androgen receptor (AR) alterations in prostate cancer. The first part of this overview summarized alterations that impact the *AR* gene. To date, somatic *AR* genomic alterations that have been described and validated in large genomic sequencing studies include *AR* copy number gain, point mutations of the *AR* gene, copy number gain of an enhancer located upstream of the *AR* gene body, and rearrangements that alter the structure of the *AR* gene. These DNA-level alterations impacting the *AR* gene are virtually nonexistent in primary PCa but are present in approximately 90% of HRPC.[23]

At the RNA level, AR mRNA alterations have been demonstrated. AR-V7 is an mRNA splice variant that has been well-described in its prediction of resistance to enzalutamide and abiraterone in mHRPC.[24] Expression of AR-V7 protein, however, was very rarely found in mHSPC and is felt to emerge primarily in the mHRPC setting.[25] Additional AR mRNA variants have been identified and shown to be expressed in HRPC, but these species have not been evaluated in mHSPC.[23]

AR transcriptional activity has been evaluated and patients with low AR activity tend to develop metastasis more quickly and demonstrate higher levels of resistance to AR-targeted therapies compared to patients with higher AR activity.[26] This was shown in treatment naïve patients and thus may be applicable to the mHSPC space.

In short, *AR* gene alterations are likely non-existent in mHSPC, though no large-scale unbiased DNA-seq studies have been performed in this space to date. The splice variant AR-V7 is nearly undetectable in HSPC tumor tissue, and low AR transcriptional output in hormone-naïve tumors may reflect reduced AR dependence and a more aggressive trajectory with reduced response to AR-targeted therapy.

RB/TP53/PTEN/SPOP IN mHSPC

Himisha Beltran provided an overview of the genomic alterations relevant to mHSPC. At the outset, she reviewed the frequency of mutations in mHSPC with TMPRSS2-ERG fusion occurring in 40%-50% (similar to localized PCa) and SPOP mutation in 5%-6% of patients. Conversely, PTEN and TP53 alterations occur in 40% and 25%-45%, respectively, approaching the frequency of mutation seen in these genes in mHRPC. Complete loss of RB1 is rare in mHSPC (compared to approximately 20% of mHRPC) whereas heterozygous loss is more common and may approach 30%. BRCA2 mutations are found in 3%-7% and CDK12 in approximately 5%, higher in *de novo* metastatic disease.[17,27-29]

There also seems to be a relation between genetic alterations and volume of disease. In a study performed by Gilson and colleagues, a feasibility and prevalence study was performed using archival primary tumor samples from 54 men in the STAMPEDE trial with *de novo* mHSPC.[27] Alterations seen more frequently in high volume disease were aberrant DNA damage repair (DDR) (22% in high volume vs 15% in low volume), Wnt pathway (16% vs 4%), and chromatin remodeling (16% vs 8%). PTEN/PI3K pathway alterations were equally prevalent between high and low volume disease and TP53 and ETS were more common in the low volume disease state (31% vs 21% and 38% vs 19%, respectively). However, the overall small numbers limited statistical comparisons.

Within the MSK cohort, high volume disease was associated with worse prognosis, more copy number alterations, higher alterations in NOTCH, cell cycle, and epigenetic modifier pathways. The population was mixed but patients with *de novo* (compared to relapsed) disease had higher CDK12 alterations though their prognosis was no different. In this cohort, alterations in SPOP and Wnt were associated with better prognosis whereas alterations in AR (rare), TP53, cell cycle, and MYC were associated with a poorer prognosis. No difference was found in PI3K pathway alterations.[28]

It is also important to consider when genetic alterations occur. TMPRSS2-ERG and SPOP have been shown to occur early in prostate cancer pathogenesis whereas DDR alterations may occur early (detectable in primary tumors) or potentially late as acquired events. Similarly, RB1, TP53, and PTEN loss can be seen both early in the disease and acquired late.[30] In a subset of patients treated on the PUNCH trial of neoadjuvant chemohormonal therapy prior to RP in clinically localized high-risk PCa, TP53 mutations were enriched in residual tumors after chemohormonal therapy potentially through clonal selection.[31] In a study by Rodrigues and colleagues published in 2019, RB1 FISH was performed for 70 samples in 41 patients including 20 matched, same-patient HSPC-HRPC pairs. Of the 20 HSPC samples, 35% had shallow RB1 deletions compared to 65% of the matched, same-patient HRPC samples.[32] These data are consistent with enrichment for RB1 deletions (mostly heterozygous) in clinically aggressive

HSPC and selection for and evolution of RB1 deletions in the development of HRPC.

In looking at RB1 specifically, loss of RB1 is associated with a poor prognosis and is seen more frequently in mHRPC. In addition to its role in cell cycle, RB1 loss can regulate tumor plasticity, differentiation, DNA repair, AR independence, and metastasis.[32-41] Loss of RB1 has been associated with sensitivity to cabazitaxel,[37] and in combination with other tumor suppressors, has been associated with sensitivity to platinum chemotherapy[42] or combined PARP and ATR inhibition.[40] The relevance of these findings in mHSPC is not known. Of note, in a randomized phase 2 study recently reported by Palmbos *et al*, the combination of ADT and the CDK 4/6 inhibitor palbociclib in RB-intact mHSPC (determined by tumor IHC) did not impact response or PFS; 97% of patients screened on this study had RB-intact. It is important to remember that there are many ways to lose RB1 pathway function[43] and it is possible that an RB1 functional signature[44] may be informative in mHSPC where homozygous deletion and protein loss are rare.

With regard to TP53, preclinical work shows that combined inactivation of TP53 and PTEN leads to abiraterone resistance[45] and combined loss of TP53 and RB1 drives AR independence and neuroendocrine differentiation which may suggest that these patients are less likely to benefit from AR-directed therapies up front.[41,46] Compound alterations of TP53, PTEN, and RB1, while enriched in advanced disease, have been associated with increased risk of relapse and death in localized HSPC.[47]

SPOP mutations, on the other hand, are enriched in localized prostate cancer (8%-10%) compared to mHSPC (5%) and mHRPC (<5%). They have been associated with androgen sensitivity and of response to AR pathway inhibition (ARPI) in mHRPC.[34,48] In mHSPC, the role has not been defined but perhaps these mutations can be used to select for patients treated with up front ARPI.

In summary, loss of tumor suppressors (RB1, TP53, and PTEN) is associated with resistance to ARPI. While the context of these alterations matter (early vs late, co-occurrence with other alterations), 1 question is whether loss of any or a combination of these can be used to select for patients who may benefit from chemotherapy earlier on. Conversely, SPOP mutation is associated with sensitivity to ARPI and may be considered to select for patients who may benefit from aggressive ARPI up front. With respect to BRCA2, MSI/MMR, CDK12, and PTEN—these are emerging as predictive biomarkers within the mHRPC space and it remains to be seen if they will be similarly predictive in mHSPC. Overall, how genomics are incorporated will need to be carefully considered as there is an opportunity to obtain data from the primary or metastatic lesion as well as ctDNA. Important factors moving forward include which is most predictive and which is most readily accessible in a trial setting.

CIRCULATING TUMOR DNA

Alexander Wyatt reviewed plasma circulating tumor DNA (ctDNA) and its role as a biomarker source in metastatic prostate cancer. In mHRPC, the ctDNA fraction (ie, tumor content as a proportion of all cell-free DNA) shows considerable patient-to-patient variability but is positively correlated with serum markers of proliferative tumor burden and the extent of metastatic disease.[49] A low ctDNA fraction prior to treatment portends a good prognosis in mHRPC and this appears to be independently prognostic when compared to other clinical features.[50, 51] Early studies suggest that the association between disease burden and ctDNA fraction will extend to mHSPC.[29] Temporal changes in ctDNA fraction during treatment may be predictive for treatment response in both mHSPC and mHRPC, similar to early PSA measurements.[29, 51, 52]

In mHRPC, ctDNA fraction as a biomarker is being studied in the PROTRACT trial (NCT04015622) where the objective is to determine whether the ctDNA fraction can aid treatment selection for second line ARPI vs chemotherapy.

In mHRPC and mHSPC with high ctDNA fractions, it is possible to perform extensive characterizations of the somatic genome, and to detect clinically-relevant alterations such as DNA repair gene defects and PI3K pathway alterations. However, a key limitation of ctDNA analysis is that not all patients have sufficient ctDNA to enable detection of copy number changes. It is important that tests discriminate between true negatives and potential false negatives due to insufficient ctDNA levels. Since treatment can rapidly affect ctDNA fraction, this discrimination is particularly relevant in mHSPC where patients may receive ADT prior to blood collection for ctDNA analysis.

Outstanding questions include whether ctDNA fraction serves as an independent prognostic indicator in mHSPC, whether the depth of ctDNA decline after initiation of treatment is predictive of durable benefit, and whether a rising ctDNA on therapy is indicative of progression to mHRPC. From a genomics standpoint, the relationship between tumor suppressor loss detected by ctDNA and prognosis, the potential for DNA repair defects detected in ctDNA to serve as a predictive biomarker for PARPi, the relationship between primary and metastatic lesions and ctDNA, and whether detection of genetic alterations associated with mHRPC can aid in identifying early progression remains to be determined.

HSD3B1 AND EXTRAGONADAL ANDROGEN DEPENDENCE

Nima Sharifi discussed the role of *HSD3B1* in prostate cancer and as a biomarker. It encodes for the enzyme 3β-hydroxysteroid dehydrogenase-1 (3βHSD1) which is germline regulated.[53] Two functional missense-encoding alleles have been described (1245A and 1245C) with

1245A considered the adrenal restrictive allele and 1245C the adrenal permissive allele. 3βHSD1 encoded by the adrenal restrictive allele is rapidly degraded and slowly converts adrenal dehydroepiandrosterone (DHEA) to dihydrotestosterone (DHT). Conversely, the adrenal permissive allele encodes for a more stable 3βHSD1 enzyme with fast conversion of DHEA to DHT and high amounts of DHT from extragonadal sources.[54]

Clinically, homozygous adrenal permissive inheritance is associated with quicker time to progression on ADT when compared to the homozygous adrenal restrictive allele, with heterozygous inheritance falling between the 2.[55] Among men with low volume mHSPC in the CHAARTED trial, inheritance of at least 1 copy of the adrenal permissive allele is associated with a shorter time to progression to HRPC and lower OS.[56] Among HRPC patients treated with abiraterone or enzalutamide, homozygous adrenal permissive inheritance was associated with 7 months shorter OS and 23 months shorter OS from the time of first-line ADT.[57] A separate study looking at mHRPC patients with mixed exposure to first- and second-line abiraterone/enzalutamide found a decreased PSA response rate in homozygous adrenal permissive men but did not demonstrate a difference in overall survival.[58]

In assessing its role as a biomarker, it is important to recognize that populations vary in the prevalence of the adrenal permissive allele. In Europe, there is higher frequency of the adrenal permissive allele (30%-40% allele frequency) compared to a lower frequency in East Asia and Africa (5%-10%). When looking at phenotypes associated with *HSD3B1*, race becomes a major confounder and needs to be accounted for.

Overall, *HSD3B1* inheritance enables gonadal testosterone independence in low volume mHSPC. It is easily assessed in the germline and those with homozygous adrenal permissive alleles may have worse outcomes even after development of HRPC. A major question moving forward will be whether the poor outcomes associated with the adrenal permissive *HSD3B1* allele are reversible with early enzalutamide/apalutamide/abiraterone in mHSPC.[59, 60]

INCORPORATING BIOMARKERS INTO CLINICAL TRIALS

Susan Halabi reviewed incorporating biomarkers into clinical trials, whereby biomarkers will be utilized for enrichment, stratification or analysis. Before designing a trial, however, one must first review the types of biomarkers which include diagnostic, prognostic, predictive (of response and resistance to therapy), and surrogate biomarkers. The goal of the biomarker will affect the design.

There are several approaches to integrating biomarkers into clinical trials designs:

- Randomize-all design in which all patients are randomized to experimental treatment or the standard of care and the biomarker is measured at baseline before random assignment. The design of the trial does not depend on the biomarker status and the association of the biomarker(s) with the clinical outcome(s) after the trial has been completed.
- Targeted design in which only biomarker-positive patients are randomized to different treatments vs standard of care.[61] Utilizing this design requires that the biomarker status is assessed prior to randomizations. This type of design is efficient if the biology and underlying mechanism of the therapy is known to work for the biomarker positive patients. Studies utilizing this design have typically only looked at 1 biomarker.
- Strategy design in which patients are randomized to marker-driven treatment (marker-positive patients given the experimental arm, marker-negative given SOC) and marker-agnostic treatment (all given SOC regardless of the marker status).[62] This design is advantageous when the prevalence of the biomarker is high and when one is testing whether the biomarker treatment strategy is superior than SOC.
- Targeted hybrid design in which biomarker positive patients are randomized to experimental vs SOC and marker negative patients are enrolled on the SOC. This has a benefit over the strategy design in that it would require fewer patients and meets regulatory requirements for drug approval in a marker-positive subpopulation, but it may require a large population to be screened in order to recruit enough marker-positive patients to meet that endpoint. Additionally, the efficacy of the treatment in marker-negative patients cannot be assessed in this design. Historically, this design has been used with only 1 specific assay looking at a single biomarker. One question is whether it could be used with multiple biomarkers or with a signature assay. Additionally, it may be interesting to consider whether treatment randomization can occur not only at treatment initiation but also at the first sign of progression. An example of a hybrid design is TAILORx trial where a classifier is used.[63]
- Stratified biomarker trials: Patients will have their biomarker status determined prior to randomization and regardless of the biomarker status they will be randomized to experimental therapy or SOC.[64] This is the only design which will test prospectively an interaction between a biomarker and specific treatment, in other words testing the predictive ability of the biomarker. The main disadvantage, however, is the power of the biomarker-treatment interaction test is low, requiring large sample sizes. Additionally, there is potential for overtreatment of marker-negative patients.
- Master and platform trials include multiple parallel drug sub-trials that are conducted under 1 protocol. These trials could be designed either as basket trials (patients with certain mutation type regardless of histology), such as the NCI MATCH (NCT02465060) and the ASCO TAPUR trials[65] or umbrella trials (often 1 histology with different molecular subtypes), such as the Lung-MAP trial.[66]

In designing a clinical trial that incorporates a biomarker key factors to consider are: the prevalence of the biomarker, the sensitivity and specificity, reproducibility and validity of the assay, the strength of evidence for the biomarker, validation of the cut-off points for the biomarkers, and the feasibility of near real-time assessment. It is evident that the "one-size fits all" design is not recommended and ultimately the best design is one that answers the primary scientific question, considers the above factors, and is feasible.

EXISTING RESOURCES AND TRIALS FOR BIOMARKER DEVELOPMENT IN mHSPC

Christopher Sweeney and Gerhardt Attard discussed some of the strategies employed in recent trials to allow for biomarker identification and validation and what resources currently exist in the mHSPC space. Firstly, defining and validating a biomarker in this space will rely on a strategic use of biospecimens. This would include consent for future use of samples, use tied to clinical trials outcomes, use of preliminary data to generate new hypotheses, and importantly the alignment of assay platforms and analyses. This has been done in CHAARTED, STAMPEDE, TITAN, and ENZAMET and allows for the initial development and training of a biomarker in 1 trial and validation in another.

Important also is the recognition of existing prognostic markers, highlighted earlier by Maha Hussain and here by Christopher Sweeney. These would include metachronous and low volume disease which has a median OS of 8 years whereas *de novo* high volume disease has a median OS of 3 years, demonstrating existing clinical parameters that are already prognostic.[67, 68] These set the bar that any biomarker should have to improve upon in order to be considered a step forward.

Questions generated by these existing trials in mHSPC include whether we can identify patients who would benefit from early docetaxel vs early potent ARPI, if we can identify patients who would benefit from triplet therapy, and whether we can identify biomarkers for more accurate prognostication and to identify additional high yield targets for drug development and next generation trials.

Among the resources built within the existing trials include a rich library of tumor, germline, and, increasingly, serum and plasma samples that may be used to answer or further develop these questions. As an example, gene expression profiling in collaboration with Decipher Biosciences on tumor samples collected in the CHAARTED and TITAN trials identified lower hazards of death when docetaxel was added to ADT in luminal B compared to basal sub-types whilst the inverse was observed in TITAN with lower hazards of progression when apalutamide was added to ADT in basal compared to luminal B.[70] Germline SNP data have also been looked at with *HSD3B1* in CHAARTED demonstrating that in low volume disease, the adrenal permissive allele seems to counter some of the OS benefit with docetaxel and ADT vs ADT alone.[56] As discussed by Nima Sharifi, this raises the question of whether early enzalutamide can overcome the poor outcome in the low volume adrenal permissive state, and this indeed will be looked at within the ENZAMET data. Circulating cytokine data is also available and has demonstrated that high IL-8 is associated with poor overall survival compared to low IL-8 in patients treated with ADT and ADT with docetaxel.[71, 72]

Ultimately, this work emphasizes the utility of aligning measures and methods across prospective trials early on and remaining consistent. By doing so, we can use our randomized cohorts to look at biological data, therapies, and identify key biomarkers and develop new therapeutic strategies.

CONCLUSION

Several first-line treatment options have been shown to be effective in men presenting with mHSPC. Concomitantly, signals have emerged identifying a number of potential biomarkers which will need to be assessed and validated for clinical practice, and to do so will require coordination to ensure a meaningful result.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2020.12.021.

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