

REPORT FROM THE 2021 ASCO GU MEETING
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“Practice-Changing Science, Evolving Care”

ASCO GU is a yearly multidisciplinary symposium with world-renowned faculty that covers relevant topics in genito-urinary malignancies. Both state-of-the-art tests and treatments, as well as new research, were presented virtually this year. Here is a Report on some of the more important presentations in Prostate Cancer.

Dr. Peter Carroll of UCSF gave a 2021 update on Active Surveillance (AS), which is traditionally used in low-low risk, low risk, and favorable intermediate-risk prostate cancer to help avoid over-treatment. Its use, however, varies widely across the country. The cautionary worry with Active Surveillance is that men will progress (be upgraded to a worse Gleason Grade Group or worse situation with long-term use). Dr. Carroll spoke of the genomic profiling that can be done for these patients; for example, the use of GPS (Oncotype Dx) combined with a CAPRA Score can help predict adverse events. That kinds of data can reveal if there is an increased risk or a decreased risk of an upgrade in disease extent; but he cautioned that the data is not absolute in and of itself, and must be used in context. Dr. Carroll said that there are several indicia in considering the appropriateness of AS, including Age, PSA Density (PSAD) less than .15; 2 negative biopsies; Serial MRI's (if the patient is not going to have a biopsy), Grade and Volume. Dr. Carroll also spoke to controversies with AS, for example, should younger patients be enrolled? He said that younger men on AS actually have a lower rate of progression. In describing pathology, he said that Gleason Grade alone is not predictive but that volume is, and that with Grade Group 4 the presence of cribriform and stromal reaction are in fact correlated with progression. One must also be careful with patients with a positive BRCA 2 mutation. Also, Dr. Carroll stated that while African-American patients do not appear to have different results with AS, he said that they represent only a small proportion of patients in these cohorts of the pertinent trials. However, Dr. Carroll cautioned that AS needs to become less burdensome for greater use.

Dr. Felix Feng, also of UCSF, addressed Molecular Signatures Associated with Long-Term Response to Apalutamide in nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC). This was a new analysis of findings from the SPARTAN Trial, a Phase 3 Trial which evaluated the efficacy of Apalutamide in combination with ADT in patients whose disease had become resistant to hormonal therapy but who did not have metastatic disease (nmCRPC). The primary

endpoint was Metastases-Free Survival (MFS). SPARTAN's final analysis showed an overall survival benefit to the Apalutamide group of 73.9 months versus 59.9 months in the placebo group. In the current analysis, Dr. Feng separated Time-to-Progression events into quartiles, defining Long Term Responders (LTR's) as those without events until the 4th quartile, and Early Progressors (EP's) having events in the first quartile. In the Apalutamide + ADT group, Increased Immune Activity, or Decreased Vascularization or Proliferative Capacity at Baseline were associated with LTR. He also mentioned that Luminal Tumors typically have a better (MFS) than Basal Tumors treated with APA + ADT, unless those Basal Tumors have a high T-Cell proliferation.

Dr. Jonathan Tward of the Huntsman Cancer Institute at the University of Utah presented the results of a study showing that a score based upon clinical characteristics along with Cell Cycle Proliferation (CCP) gene expression can provide accurate information on prognosis in terms of the 10-year risk of metastasis in patients with intermediate- and high-risk localized prostate cancer. The Combined Clinical and Cell-Cycle Risk (CCR) score combines a CCP Score from Myriad's Prolaris test (31 CCP genes) with clinical indicia. This was a validation study; a prior development study had found that a CCR score cutoff of 2.112 could identify patients who had less than a 5% risk of metastasis at 10 years, regardless of use of ADT or NCCN risk group. Thus, importantly, those patients with a risk of metastasis less than 5% can be counseled that the use of ADT may not be clinically significant, thereby avoiding its use.

Good news from the Radiation Therapy and Theranostics field. The Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) announced results of the TheraP Trial, which compared 177Lu-PSMA-617 (Lu-PSMA), a novel radioactive treatment, to the current standard-of-care chemotherapy (Cabazitaxel) for men with metastatic castration-resistant prostate cancer. This study utilized Theranostics, first mapping the cancer with a PET scan, and then treating the men with radioactive Lutetium-177 attached to a similar molecule as that used for the PET scan. The primary endpoint was to assess change in PSA following treatment; a favorable response was defined as a reduction in PSA of 50% or more. This reduction occurred in 66% of the men who received Lu-PSMA compared to 37% in those men who received cabazitaxel. The Lutetium patients also had fewer adverse events than the Cabazitaxel group. The Chair Professor Ian Davis said that "TheraP is the first trial in the world comparing Lu-PSMA to an active and effective treatment and has provided evidence that Lu-PSMA might be a good alternative option to chemotherapy for men with advanced and pre-treated prostate cancer."

And again, in a plenary abstract in the Poster Highlights Session, a report was made on a prospective Phase II/III Study of PSMA- Targeted 18F-DCFPyl -PET/CT in patients with prostate cancer (OSPREY). PSMA-imaging is very promising for prostate cancer detection, with higher

sensitivity, specificity, and accuracy. 18F-DCFPyL is a new PSMA-targeted radiopharmaceutical for PET; on the basis of the data presented in the Poster, it was concluded that “18F-DCFPyL-PET/CT may be a useful tool in staging men with both metastatic and nonmetastatic relapsed prostate cancer”. And in a separate presentation entitled the “Wild West”, Dr. Declan Murphy of Australia expounded on how outstanding PSMA-Gallium (just approved in the US) is for imaging in prostate cancer. In Australia they have been using it for 6 years.

In the field of testing, Foundation Medicine and collaborators announced that a new study continued to demonstrate the clinical utility of Blood-Based Comprehensive Genomic Profiling (CGP) in patients with advanced prostate cancer. Their study evaluated genomic alterations which were identified using liquid biopsy in over 3,000 patients, and also looked at concordance with liquid and tissue biopsy in over 800 patients. There was high concordance between targetable alterations utilizing circulating tumor DNA (ctDNA) and tissue-based comprehensive genomic profiling (CGP) in patients with metastatic castrate-resistant prostate cancer. In many patients it was found that liquid biopsy detected more acquired resistance mechanisms than were detected by tissue biopsy. Dr. Geoff Oxnard of Foundation Medicine stated that “When tumor tissue is difficult to obtain, as is often the case in patients in mCRPC, liquid biopsy is a proven, minimally-invasive method to secure genomic insights, with the option to reflex to a tissue biopsy if ctDNA turns out to be insufficient to analyze.”

Two other studies examining genomic analysis of circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) in advanced prostate cancer were also presented. In one of the studies, BRCA mutations were found in both liquid biopsies and in tissue; a comparison was made. The prevalence of BRCA 1 mutations was much higher in the liquid biopsy specimens; the opposite was true with BRCA 2 mutations. In the other study, genomic analyses were performed of 3,334 patients with advanced prostate cancer using ctDNA from the TRITON23 Trials and routine comprehensive genomic profiling. Dr. Hanna Tukachinsky of Foundation Medicine stated “...the majority of patients with advanced prostate cancer have abundant ctDNA that can be tested using comprehensive genomic profiling to support doctors as they consider targeted therapies for their patients...”. She also stated “Although a large proportion of patients in this study had detection of BRCA alterations in both their tissue and liquid biopsies, some patients had no sign of BRCA alteration in their tissue biopsy taken years earlier, while having a high variant allele frequency of BRCA alteration in liquid. These patients could benefit from treatment with PARP inhibition.”

Speaking of PARP Inhibition, a gene-by-gene analysis of DNA repair mutations in patients with mCRPC in PROfound, a Phase III study, found that patients with BRCA alterations had the most important antitumor activity on Olaparib. The study points out the importance of genetic testing for all patients with high-risk mCRPC and highlights the potential overall survival

(OS) benefits of treatment based upon that testing. Genetic counseling is also advised. And in a Randomized Phase 2 trial reporting out of UC San Diego, investigators did a biomarker analysis of Olaparib with or without cediranib in men with metastatic castrate-resistant prostate cancer (mCRPC). Recently two PARP inhibitors have been approved in mCRPC for men who had certain gene alterations associated with homologous recombination deficiency: Olaparib and Rucaparib. This Study compared Olaparib, with Olaparib in combination with cediranib, an oral antagonist of VEGF receptors. There were a total of 90 patients, most of whom (unlike in PROfound) were heavily pre-treated. One arm received the standard dose of Olaparib (300 mg twice a day) and the other arm received cediranib plus a reduced dose of Olaparib. Crossover was permitted from the Olaparib-only arm to the other combination arm at time of progression. The primary outcome was met: an improved radiographic progression-free survival (rPFS) in pretreated mCRPC, independent of homologous repair gene status, although the benefits appeared stronger in those patients with tumors deficient in homologous recombination.

The SAKK 09/10 randomized Phase III trial was also presented at the Meeting, comparing a dose-intensified approach to salvage radiotherapy versus a conventional dose. The new study showed that the dose-intensification was not superior in patients with biochemically recurrent prostate cancer who had undergone a radical prostatectomy. 170 patients received 64 Gy and 174 received 70 Gy. The study did not meet its primary endpoint: freedom from biochemical progression. Additionally, there was no difference in progression-free survival or time to ADT.

The ACIS study was a randomized, placebo-controlled double-blind Phase 3 Study of Apalutamide and Abiraterone plus Prednisone (AAP) or Abiraterone plus Placebo and Prednisone. In other words, 982 patients were randomized to receive abiraterone and Prednisone with or without Apalutamide. Baseline characteristics were similar in both groups. The overall data showed that the Trial met its primary endpoint of Radiographic Progression-Free Survival (rPFS); this primary endpoint was met with benefit with AAP (a 30% reduction); however, after 54.8 months of median follow-up, although overall survival was numerically higher it was NOT statistically significant. Other secondary endpoints were also similar. It is interesting to note that more patients who also had Apalutamide had at least a 50% decline in PSA levels, and in fact undetectable PSA levels at some point during their treatment. But the median time to PSA progression did not differ between the two groups. While there were no unexpected adverse events (AE's), those who received Apalutamide had more fatigue, hypertension, skin rash and cardiac disorders. Questions remaining from the trial: whether Apalutamide's androgen signaling inhibition means better outcomes for patients, and whether or not androgen inhibition after progression is helpful for those patients.

Final Results of the Phase 3 TITAN study were presented, and demonstrated the continued statistically significant benefit of adding ERLEADA (Apalutamide) to ADT in overall survival (OS) in patients with metastatic castration-sensitive prostate cancer (mCSPC), no matter the extent of disease, when compared to Placebo plus ADT. Dr. Kim Chi, principal investigator of the TITAN Trial, stated, “The TITAN final analysis further confirms that treatment with apalutamide can prolong overall survival and offer a clear long-term clinical benefit and established safety profile for patients with metastatic prostate cancer who are starting androgen deprivation therapy. Based on these data, ADT alone should no longer be considered sufficient for patients with advanced, castration-sensitive disease.”

Another interesting presentation from Dr. Felix Feng at UCSF discussed the Decipher Test as a guide to post-surgical therapy in prostate cancer. He showed that scores with the 22-gene Decipher Genomic Classifier (GC) were independently associated with risk for metastasis, prostate cancer-specific mortality, and overall survival (OS) among patients with recurrent disease who were treated with salvage radiation therapy with or without bicalutamide. The results are important in that they mean that **not all men with biochemically recurrent disease (BCR) after surgery will benefit from hormone therapy.** This was also an ancillary study of the NRG/RTOG 9601 Randomized Clinical Trial and was published in JAMA Oncology online on February 11, 2021. The findings as described by Dr. Feng will likely help with shared decision-making between physician and patient. Dr. Feng noted that the findings of the study can be quickly incorporated into clinical practice. He stated the importance of personalizing all therapies for men with prostate cancer.

In a panel presentation, Dr. Michael Morris of Memorial Sloan-Kettering Cancer Center asked about patients with low-risk disease but BRCA pathogenic mutations? Should there be prophylactic strategies for treatment? And who should be referred for genetic testing? He concluded, to answer that: Yes, for patients with a personal history of high-risk disease or metastases; and/or patients with a family or personal history of cancer (eg, associated with either BRCA 1 or 2, Lynch Syndrome or HOXB 13 positive). He might suggest tumor-only sequencing with BRCA 1 or 2 or other mutations. He referenced the NCCN Hereditary Cancer Guidelines and non-prostate cancer risks and screening for BRCA 1 and 2 positive men. Dr. Morris stated that about 17% of men with localized disease have germline mutations predisposing them to prostate cancer. His work that was presented was also published in JAMA Oncology that day. Dr. Morris stated that the median survival time is 5 years in carriers, and 16 in non-carriers, showing the aggressivity of the BRCA mutation. He then referenced the study in *European Oncology* which showed that positive BRCA status is about 3 times the increased risk of metastases and prostate cancer-specific mortality than non-carriers, but that 75% of men with BRCA 1 or 2 germline mutations will not be diagnosed with prostate cancer. There was

also discussion of monoallelic loss versus biallelic loss. Lastly, Dr. Morris stated that there is no indication that BRCA-mutated tumors are more radio-sensitive.

A “Real-World Evidence Study” presented by Dr. Stephen Freedland looked at how men in the Veterans Health Administration have received treatment over the past 15 years, given all of the developments in prostate care during that time. The investigators identified patients with metastatic castration-sensitive prostate cancer who had ADT alone or ADT with anti-androgen, docetaxel, or abiraterone between April 1, 2014 and March 31, 2018. Their data obtained showed that most patients with mCRPC in the VA System were treated with ADT only, even though there is Level 1 evidence supporting the use of docetaxel and Novel Hormonal Therapies (NHT’s).

In a retrospective study out of France, researchers queried whether Overall Survival (OS) in mCRPC could be improved with multiple cabazitaxel rechallenges. Currently cabazitaxel is typically utilized in the second-line chemotherapy setting. A presentation in the Poster Highlights Section at ASCO GU looked at the feasibility and efficaciousness of multiple cabazitaxel challenges in these mCRPC patients. The conclusion of these investigators was that repeated rechallenges with cabazitaxel may extend Overall Survival (OS) without unmanageable toxicities.

In metastatic castration-resistant prostate cancer (mCRPC), a study out of the University of Michigan showed that a new oral docetaxel formulation known as ModraDoc006, when combined with ritonavir, had definite advantages over IV chemotherapy for these patients – it was convenient, taken by mouth, and better-tolerated. ModraDoc006 was given twice a day (20 mg and 200 mg of ritonavir) along with 5 mg of oral prednisone. Another benefit of oral administration was seen because of the pandemic. Use of the oral agent avoided the risk of infection from cytopenias and neuropathy, frequently seen with IV docetaxel. The primary endpoint of the study was radiographic progression-free survival (using criteria from the Prostate Cancer Working Group 3). Study investigators are optimistic about the drug development of this agent, which had “a favorable toxicity profile and comparable efficacy.”

Poster Sessions also had some interesting reports and findings. For example, Genomic Health Incorporated (Exact Sciences) posited that “Adverse pathology at radical prostatectomy is highly associated with future development of metastasis and prostate cancer mortality and may be used as a short-term predictor of outcomes.”UCLA presented a Poster on “Association of reductions in PSA screening across states with increased metastatic prostate cancer” and concluded: reductions in PSA screening may explain some of the recent increase in metastatic prostate cancer at diagnosis in the United States...a worrisome consequence that needs attention...we support shared-decision making policies, such as the 2018 USPSTF update, that may optimize PSA screening utilization to reduce the incidence of metastatic prostate

cancer in the United States.”Another Poster reported on a group that evaluated the prevalence of homologous recombination repair gene (BRCA 1/2 and ATM) mutations (HRRm) in a real world prostate cancer population that had commercially available cfDNA assay results available. The poster postulated that there is a rationale for utilizing cfDNA comprehensive genomic profiling as a routine test for detection of HRRm to identify those who are appropriate candidates for PARP Inhibition.

Another significant Poster presentation was submitted by Johns Hopkins, looking at cell cycle progression score and PTEN as prognostic factors for metastasis in intermediate- and high-risk prostate cancer overall. These had never been evaluated together as prognostic markers for risk of metastasis in a radical prostatectomy cohort of men with NCCN intermediate- or high-risk prostate cancer, nor in those patients who also received salvage radiation therapy alone or with androgen deprivation. Conclusion: CCP score, but not PTEN, was significantly associated with metastasis-free survival. Myriad Genetics participated.

Other Poster Sessions: “Adverse pathology at radical prostatectomy is highly associated with future development of metastasis and prostate cancer mortality and may be used as a short-term predictor of outcomes.” (Genomic Health, an Exact Sciences corporation)

Lastly, there were a few Posters on the use of Darolutamide (Nubeqa). One examined the safety of Darolutamide (DARO) for non-metastatic castrate-resistant prostate cancer (nmCRPC) as an extended follow-up to the ARAMIS Trial. Darolutamide remained well-tolerated. And looking at the effect of crossover from placebo to Darolutamide on overall survival (OS) in the ARAMIS Trial, the conclusion was “Early treatment with DARO in men with nmCRPC is associated with significant improvement in OS regardless of pts crossing over from PBO to DARO. The safety profile of DARO remained favorable at the final analysis.”

Although ASCO GU 2021 was a virtual, not an in-person Meeting this year, attendees received an abundance of excellent scientific results in prostate cancer, learned about interesting trial results, heard from superb speakers, and were encouraged about the future of targeted therapy in prostate cancer.

Next year in person in San Francisco at ASCO GU 2022!