REPORT FROM ASCO 2018

The 2018 American Society of Clinical Oncology Meeting took place in Chicago June 1-5, 2018 and I attended the entire Meeting. Unlike some past ASCO Meetings (including the ASCO Genito-Urinary Cancers Meeting ("ASCO GU") held in February of this year, there were no earth-shattering dramatic findings or clinical trial results to report. There were, however, some interesting findings and hopeful news that need further investigation and research. Additionally, we learned that Dr. Bruce Johnson, President of ASCO and a lung cancer specialist, was recently diagnosed with prostate cancer, and in his Presidential Talk during a plenary Session, he told the attendees what it was like to be a cancer patient and how it has impacted him. At that session we were also fortunate to hear from Dr. Norman Sharpless, the new head of the National Cancer Institute; and from Dr. Scott Gottlieb, new Commissioner of the FDA.

Some interesting talks were "Immunotherapy Beyond the Checkpoints: CARS, trucks and More" from Dr. Carl June; "Metastatic Prostate Cancer Tumor Board: Optimizing Patient Selection and Treatment"; and an Oral Abstract Session on Prostate Cancer.

In a Phase III Trial from the Scandinavian Prostate Cancer Group (SPCG-13), findings presented showed that adjuvant chemotherapy (docetaxel) without prednisone did not improve biochemical disease-free survival in men with intermediate-risk or high-risk prostate cancer who have undergone radical radiation therapy with ADT (androgen deprivation therapy). In Arm A of the Trial men received 6 cycles of adjuvant docetaxel without continuous prednisone, and in Arm B there was only surveillance of the patients. After 5 years, there was no disease progression observed in 69% of pat8ents in Arm A and in 69.7% of patients in Arm B. There was no difference in the primary endpoint between the Arms. In analyses, Gleason Grade looked to be the only factor predictive for progression; and a sub-group analysis there was a trend favoring docetaxel for patients with a Gleason greater than 8, but the P value was not statistically significant.

Reports on the PROSPECT Trial were disappointing: there was no overall-survival benefit seen for patients with asymptomatic or minimally-symptomatic metastatic castration-resistant prostate cancer (CRPC) who were treated with the PROSTVAC-V/F (PRO) cancer vaccine, compared with placebo. The Phase II trial had shown an 8.5 month improvement in survival (OS), but after three interim analyses of the data from the Phase III trial of PRO, the data monitoring committee recommended that the PROSPECT Trial be closed down. These results were presented by Dr. James Gulley (Building 10 at NIH) who presented at NASPCC"s 13th Annual Meeting and who is scheduled to return to give us an update on Immunotherapy in Prostate Cancer at this year's 14th Annual Meeting. While overall survival in all arms was approximately 1 year longer than anticipated, it was surmised that that was because of improved standard of care. One of the commenters suggested that we need to make prostate cancer more immunogenic to checkpoint inhibitors and vaccines so that we can see the same

results with immunotherapy that we have seen with other cancers. Now at ASCO 2018 Dr. Gerhard Attard reported on the Health-related Quality-of-Life (HRQL) and pain evaluations of the men in the PROSPER Trial. Results were similar in both the enzalutamide and placebo arms. Based upon all of the results, Dr. Attard reported that along with the PROSPER results and the results from the SPARTAN Trial (using apalutamide), men in the non-metastatic, castrate-resistant space.

A very exciting area of research involves the interim results of a Phase II trial utilizing Lutetium-177-PSMA617 (LuPSMA). LuPSMA is an anti-prostate-specific-membrane antigen (PSMA) monoclonal antibody combining the precision of those antibodies with anti-tumor effects of Beta radiation. PSMA is restricted to the prostate membrane and is overexpressed 100-1000 time in prostate cancer. So the thought is that since it can be detected with RT-PCR assays in the blood it may be able to be used as a marker or micro-metastatic disease. Lutetium-177 is then used as an imaging agent. In the Phase II study, patients were given Lu-PSMA-617 four cycles at six weekly intervals. PSA response was the primary endpoint. There were high response rates (82%) with a very favorable profile of adverse events (AE). These results have now led to a current Phase III Trial, VSION, which will compare patients receiving Lu-PSMA-617 plus best supportive care alone or with a novel anti-androgen axis drug, compared to best supportive care alone. There is also now the ANZUP/PCFA TheraP trial which will compare Lu-PSMA-617 with cabazitaxel.

Another discussion on the Phase III SPARTAN Trial took place at ASCO 2018. Dr. Matthew Smith and colleagues discussed the SPARTAN results that had been presented at ASCO GU in February 2018. In February the results showed that apalutamide decreased the risk of metastasis or death by 72% and prolonged metastasis-free survival by more than 2 years in men who had high risk but non-metastatic CRPC. The subject at ASCO 2018 presented by Dr. Smith was the time to metastasis and site of metastasis in patients with non-metastatic CRPC. He assessed the relationship between time to metastasis and the site of metastases after androgen-deprivation therapy (ADT) plus apalutamide or placebo. The patients that developed metastases were: Nodal: apalutamide 30% versus placebo 40%; Bone: apalutamide 57% versus placebo (52%); and Visceral: apalutamide 13% versus placebo 8%. So the SPARTAN study confirmed that apalutamide markedly decreased the risk of time to metastasis, regardless of site.

A subject of intense interest is the use of PARP Inhibitors in prostate cancer. There are approximately 450 genes that associated with DNA Damage repair (DDR) whether single strand break or double strand breaks. In tumor cells with mutated RCA ½ genes, PARP Inhibitors cause synthetic lethality and the disintegration of the tumor cell. In men with advanced prostate cancer, there is increased frequency of mutations; about 21% of men with CRPC have genetic somatic alterations and 11.8% of metastatic prostate cancer patients have germline mutations. Some data suggests that approximately 10% of patients with localized prostate cancer actually

have prostate cancer that harbors germline mutations.

The talk on PARP Inhibitors was especially fascinating. Their use has appeared beneficial in cancers with genetic origins, such as BRCA 1 and 2. The theory is that PARP – the Poly (ADP-ribose) polymerase complex begins repair of damage to a single strand of DNA, and that PARP Inhibitors are given, they cause the DNA repair to stall, causing damage and death to the cell. Normal cells appear to survive but the tumor cell disintegrates. Approximately 21% of men with castrate-resistant prostate cancer have genetic somatic alterations, and 11.8% of metastatic prostate cancer patients have germline mutations; and there has also been a suggestion that about 10% of men with localized prostate cancer have germline mutations. With advanced prostate cancer more and more men are seen to have mutations. The presence of DNA damage repair mutations (DDR) may be associated with worse outcomes in patients who are treated with abiraterone /enzalutamide. With this background, it is crucial to understand the importance of genetic testing, especially in the following situations: A known family mutation in a "cancer susceptibility gene"; a family history that suggests a hereditary prostate cancer syndrome or a hereditary breast/ovarian cancer syndrome; and tumor sequencing testing that reveals mutations in hereditary cancer risk genes, such as BRCA ½, ATM, MSH2, MSH6, MLH1 or PMS2. In fact, NCCN (National Comprehensive Cancer Network) recommends genetic testing in all metastatic prostate cancer patients. As yet, though, there remains no overall agreement whether to test routinely for these mutations in all men, even men with high risk localized disease. The topic is fascinating. There is currently a Phase II trial called the TOPARP Study involving men with metastatic prostate cancer whose disease has progressed after 1 or 2 lines of chemotherapy. The study uses Olaparib as the PARP inhibitor. 16 of 49 patients showed a response to the drug. Many single agent PARP inhibitors are being studied, and there are ongoing combination trials as well, combining PARP inhibitors with abiraterone, chemotherapy and checkpoint inhibitors. NASPCC is proud to have hosted a webinar on May 9 of this year on "Genetic Testing and Genetic Counseling in Prostate Cancer" and it is archived on our website, www.naspcc.org.

Other interesting studies presented included worldwide studies on sequential use of new agents in metastatic CRPC and a Phase II, randomized 3-arm study of Abiraterone with Prednisone, with or without Degarelix, and Degarelix alone. And of course, mirroring NASPCC's April Webinar on "AR-V7 Splice Variant and Treatment Choices in Prostate Cancer", data was presented at ASCO 2018 on that topic, showing that men with the AR-V7 Splice Variant did better with chemotherapy than the androgen receptor drugs such as abiraterone or enzalutamide. Our April Webinar also is archived on the www.NASPCC.org. There are currently 2 tests on the market for detection of this Splice Variant, one from Epic Sciences and one from Johns Hopkins.

ASCO 2018 was an exciting Meeting with a variety of reports and research presented.

Respectfully submitted, Merel Nissenberg, President, NASPCC