



REPORT FROM THE 2018 ASCO GENITOURINARY CANCERS MEETING

SAN FRANCISCO, FEBRUARY 8-10, 2018

As President of NASPCC, I attended this year's ASCO GU Meeting in San Francisco last week. There was much excitement leading up to the Meeting as there would be presentations on a new drug waiting for approval in prostate cancer or new uses for currently approved ones.

Because metastasis is a major cause of morbidity and mortality, there is a need, currently unmet, to prevent or at least delay metastasis. Two dueling presentations dealt with clinical trials with an androgen-signaling inhibitor in non-metastatic castration-resistant prostate cancer. The first report was presented by Maha Hussain, M.D. on the Phase III PROSPER Trial, one of the two placebo-controlled trials in which men with non-metastatic castrate-resistant prostate cancer (nmCRPC) were administered enzalutamide 160 mg/day + ADT versus a placebo + ADT. Enzalutamide in this group delayed the development of metastatic disease and it is hoped may therefore prolong survival. There were 1401 patients randomized 2:1 to receive enzalutamide along with ADT, versus the placebo group that received ADT alone. Metastasis-free survival (the time from randomization until either radiographic progression or death within 112 days of stopping treatment) was 36.6 months for the enzalutamide group versus 14.7 months for the placebo group. There were several subgroup analyses and the enzalutamide group did better in every category than the placebo groups.

The other results were presented by Dr. Eric Small of UCSF, who reported on the Phase III SPARTAN Trial. The next-generation androgen-signaling inhibitor, Apalutamide 240 mg/day + ADT versus ADT alone was analyzed in 1207 patients. The primary endpoint was metastasis-free survival (MFS) and, after assessment, the patient could receive a second therapy at the physician's discretion including open-label abiraterone plus prednisone, after which a second PFS assessment would be made. The median MFS in the apalutamide group was 40.5 months versus 16.2 in the placebo group. Most of the subgroups also had favorable results. Based on the data, the independent safety monitoring committee recommended unblinding the study

and allowing placebo patients to switch to apalutamide. Time to metastasis was also better in the apalutamide group.

Discussant Dr. Philip Kantoff of Memorial Sloan-Kettering urged caution; he said that it is a serious step to treat asymptomatic men with drugs that may cause severe adverse events and therefore it requires a very serious burden of proof.



Another presentation on prostate cancer by Dr. Nicholas James covered the STAMPEDE Trial which involved the addition of docetaxel to first-line long-term hormonal therapy. Results should be of help to clinicians when they are treating patients with newly metastatic, hormone-sensitive prostate cancer in deciding whether to use docetaxel or abiraterone. The side effects of docetaxel were suggested to have a longer-term benefit. A follow-up presentation on olaparib and durvalumab in men with CRPC seemed to at least partially enhance Progression-Free Survival (PFS) in patients already treated with enzalutamide and/or abiraterone. However, the Discussant on these presentations suggested that mutational load correlates with the activity of checkpoint inhibitors, a theory we also heard at our 13th Annual Meeting last October.

The Keynote lecture in prostate cancer on Thursday, February 8 was delivered by Dr. Robert Bristow of the UK, on understanding germline (inherited) and somatic changes that occur in both primary prostate cancer and/or the metastatic disease that develops.

Dr. Bristow's main point dealt with what is called oligometastatic disease in prostate cancer, where there may be anywhere from 1 to 5 small metastatic lesions present but undetected except on a bone, tMRI or PET-PSMA full body scan. His major point was that if the patients are imaged and found to have these 1-5 small lesions, there would be a need to treat them systemically; not only would this imaging help distinguish them from both patients with widespread metastatic disease and those patients who truly have only localized disease, it might be life-saving for them because the advanced disease would be more timely treated. Dr. Bristow also advised that we need companion diagnostics for cancer biomarkers in both the blood and primary tumor. Dr. Bristow added that it is still up in the air as to the sequencing and combination of prostate cancer therapies, a problem continuing to plague physicians. He stated, "We do not know necessarily how we should sequence chemotherapy, immunotherapy, next-generation hormone therapies, or molecular-targeted therapies in a patient with metastatic disease".



Other topics at ASCO GU on prostate cancer included genomics and genomic testing, along with a mention of some of the current tests on the landscape such as Decipher (Genome Dx), Oncotype Dx GPS (Genomic Health) and Prolaris (Myriad Genetics). As we have heard, genomic classifiers can be of assistance in differentiating favorable from unfavorable intermediate risk prostate cancer and therefore be of prognostic significance in deciding on treatments. For example, patients with a higher genomic classifier score with the Decipher test undergoing adjuvant or salvage radiotherapy had higher evidence of metastasis at 5 years. With Prolaris, the proliferation score may be prognostic for radiotherapy and radical prostatectomy

patients. It was concluded that combining mpMRI (multi-parametric MRI) with genomic biomarkers gives us additional and crucial information. This is especially important because of intraprostatic heterogeneity.

Additional talks included the topic of the tumor microenvironment – a stromal versus an epithelial signature. A currently engaging theory is that hypoxia leads to an early relapse. With hypoxia AND genetic instability one finds a higher relapse rate and an adverse prognosis.

Last but not least, the new information about inherited DNA and gene mutations, such as BRCA 1 and BRCA 2, is extremely significant not only for the patients themselves but for their families. It was suggested that there is a need for genetic counselors in the clinic. It was also noted that 10-12% of metastatic CRPC might be related to germline (inherited) DNA repair/ mutations, less with localized disease. In fact, a positive BRCA 2 mutation appears to be the most deleterious, leading to aggressive prostate cancer. It was pointed out that we need biomarkers-driven trials. Targeting hypoxia in these patients might include a PARP Inhibitor (PARP) such as Olaparib, which reduces hypoxia and metastatic capability. The best imaging necessary to validate these genetic studies would be PSMA, total body MRI and mpMRI.

Lastly, there were some excellent articles which appeared in the Daily News handed out at the ASCO GU Meeting, including an Expert Editorial with Dr. James Gulley (of Building 10 at NIH) as one of the two Experts in “Optimizing Immunotherapy in the Cold Prostate Cancer Microenvironment”. Dr. Gulley spoke at NASPCC’s 13th Annual Meeting last October and is planning to present again with an update at this year’s NASPCC 14th Annual Meeting scheduled for October 12-14, 2018 in Washington, D.C. on Capitol Hill again. As stated in the Daily News, “The prostate cancer tumor microenvironment may lack a sufficient immune presence, which could explain why immune checkpoint inhibitors have been ineffective as monotherapy in prostate cancer... Therapeutic cancer vaccines may be one option to drive immune cells to the tumor microenvironment through activation against a specific tumor antigen...Using immunotherapy earlier in the disease process when tumor volume and associated immune-suppressive mechanisms are lower may be advantageous...The immunotherapeutic strategies that may yield the greatest impact on patients may require multiple strategies combined together, including vaccines, immune checkpoint inhibitors, and immunocytokines.”

This was an exceptionally instructive ASCO GU!

---Merel Nissenberg, President, NASPCC