A Very Concise Synopsis of PSMA Theranostics in mCRPC
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The landscape of imaging and treatment of metastatic castrate-resistant prostate cancer (mCRPC) is evolving rapidly. One major contributor to the current excitement in the field has been the development of ligands targeting the prostate-specific membrane antigen (PSMA) which is upregulated in advanced prostate cancer (PC). PSMA, also known as folate hydrolase I or glutamate carboxypeptidase II, is a type II, 750-amino acid, 110-120 kDa, transmembrane protein expressed in the secretory cells of the prostate epithelium as well as non-prostate tissues including lung and breast) malignancies (1). In PC, the PSMA cleavage of vitamin B9 (folic acid) stimulates oncogenic signaling through glutamate receptors with downstream activation of the PI3K-Akt-mTOR signaling pathway (2).

There have been reports of several PSMA-based ligands including $^{89}$Zr- and $^{64}$Cu labeled anti-PSMA antibody and antibody fragments, $^{64}$Cu-labeled aptamers, and $^{11}$C-, $^{18}$F, $^{68}$Ga-, $^{64}$Cu-, $^{44}$Sc-, and $^{86}$Y-labeled low molecular weight inhibitors of PSMA. The FDA-approved $^{111}$In-capromab pendetide (ProstaScint) was not widely used clinically due to its relatively poor diagnostic performance, since it targeted the intercellular epitope of PSMA that are available only in dying or dead cells and generally not accessible in viable living cells. Recent strides in synthesis of small-molecule inhibitors of PSMA, for example, consisting of glutamate-urea-lysine moieties targeting the extracellular epitope of PSMA have

demonstrated major potential utility in targeted radionuclide imaging and treatment (theranostics) of metastatic PC (3). Most studies have reported on $^{68}$Ga-PSMA-11 (aka. HBED-CC)(3). Other PSMA-based radiotracers include $^{68}$Ga-PSMA I&T (imaging and therapy), $^{68}$Ga-PSMA-617, and more recently $^{18}$F-DCFPyL and $^{18}$F-PSMA-1007. Many studies have generally shown superior diagnostic performance of these radiotracers over other relevant radiotracers in the clinical settings of intermediate-high risk primary cancer, biochemical recurrence after definitive therapy, and delineation of extent of metastatic disease and patient eligibility for PSMA-targeted radioligand therapy (5, 6). It must be noted that false negatives and false positives can occur with PSMA PET (7). There is also literature on proposed procedure guidelines and interpretation and reporting standards (8-12). A number of studies have reported on major impact of PSMA PET on management of patients with PC although potential influence on outcome will need additional investigations (13-15).

PSMA is also a useful target for radionuclide therapy with beta particles (e.g. $^{177}$Lu-PSMA-617) or alpha particles (e.g. $^{225}$Ac-PSMA-617). Many studies, mostly from Germany, have shown remarkable responses in some patients heavily pre-treated for widespread metastatic disease. The German multicenter study in 145 patients with mCRPC who underwent $^{177}$Lu-PSMA radioligand therapy (RLT) reported a PSA decline $\geq$50% and any PSA decline in 45% and 60% of patients, respectively (16). Presence of visceral metastases and alkaline phosphatase $\geq$220 U/L predicted poorer response to PSMA RLT. Significant
(grade 3 and 4) hematoxicity was noted in 3-10% of patients. Transient or mild xerostomia was present in 8% of patients. Of various remedies that have been attempted in reducing the incidence of xerostomia, botulinum toxin injection in the salivary gland appears to be a promising effective method (17). No major renal toxicity was seen, although negative predictors for renal toxicity may include age > 65 years, hypertension, and history of renal failure (18). Preliminary data on the impact of PSMA RLT on overall survival is encouraging with a PSA decline of about 20% shown to be the optimal predictive parameter in the multivariate analysis of patients pretreated with at least one line of chemotherapy and abiratoerone and/or enzalutamide (19). Further observations have revealed that although about 30% of patients may not respond to the first cycle of PSMA RLT, additional therapy cycles should be still performed since nearly one-third of those patents will show a delayed response (20, 21).

It is clear that PSMA theranostics is here to stay and will likely play a major role in the management of patients with mCRPC. It is hoped that of the several imaging agents that have been evaluated, the most optimal agent will emerge that will become approved, available, and accessible. With regards to RLT, randomized clinical trials are under way (e.g. TheraP, VISION) to clearly establish the place of this treatment in the management algorithm of men with mCRPC.
Figure 1 – MIP images of sequential Ga68 PSMA PET/CT scans of a 70 year-old gentleman with a history of PC status-post androgen deprivation therapy (2008 to 2009), Lu177 PSMA PRRT (in January 2018 and March 2018).

Figure 2 - Ga68 PSMA scans on January 2018 and April 2018 noted some response in April but overall progression with new PSMA-avid bone lesions (solid arrow) and was switched to chemotherapy (from March 2018 to August 2018).

Figure 3 - Follow up Ga68 PSMA scans in June 2018 and August 2018 showed further progression of disease on chemotherapy.
References