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Attaining Precision Therapy in Prostate Cancer: A tall order

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Recent advances in technology have led to an explosive growth of information albeit not readily translatable to benefit for our patients

Prostate Cancer is arguably a quintessential example of this ‘current state of affairs’. A disease with a well understood heterogeneity that is not only inter- and intra- patient but also temporal (logothetis et al cancer discovery 2013) thus limiting our ability for ‘shotgun’ drug development. Following the successful use of this approach and registration of agents such as novel androgen signaling inhibitors (abiraterone and enzalutamide), cabazitaxel, alpharadin and sipuleucel- T (Ryan et al, De Bono et al, Kantoff et al, Hoskin et al) we have more recently met with consecutive failures (Smith et al, Beer et al, Sternberg et al). Importantly drug development of these agents (namely, cabozantinib, tasquinimod and ipilimumab) was instigated by robust preclinical mechanistic translational and early clinical data with one major caveat: Heterogeneity was not taken into consideration and that appears to be the major contributing factor to these negative trials

In the case of the perplexing PI3K pathway and its role in Prostate Cancer regardless of over 1000 published manuscripts a lot remains to be determined.

Based on very elegant preclinical work (Carver et al) and the incidence of PTEN loss in advanced disease (TCGA, and Cell paper) we are presuming that the combination of a PI3K inhibitor with a novel androgen signaling inhibitor will lead to a synergistic effect overcoming an important pathway of resistance.

The two papers presented by Massard et al and Armstrong et al showcase the cumbersome path to clinically attain this goal.

Drug-Drug Interactions such as found between buparlisib and either abiraterone acetate or enzalutamide likely impacted pharmacodynamic (PD) effect of the agent, thus potentially limiting antitumor effect. Ideally the authors would have conducted this trial introducing serial sampling of tumor to allow for assessment of PD effect on both the PI3Kinase pathway through pS6kinase status to further troubleshoot and address concern regarding agent activity.

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Neither of two trial provides us the opportunity to learn more from of potential association of PI3K pathway status at baseline or even from archival tissue though given temporal heterogeneity this may not be representative of pretreatment status.

Patients participating in these trials had far advanced disease and we can presume that the landscape of somatic alterations should have been equally enriched as that presented by the International stand up to cancer team (Robinson et al) from a similar cohort of patients. With that understanding the main question is in such a highly enriched landscape how feasible is it to identify the driver and importantly what methodology should be employed, a tissue or a liquid biopsy? The plot thickens when intra tumor heterogeneity is taken into consideration.

In essence would the answer for a path to precision be earlier treatment thus reducing “variables” that may be driving progression or resistance?

The TCGA data would suggest that indeed earlier disease is more limited in molecular alteration suggesting that a linear approach maybe feasible.

This is supported by our work (Efstathiou et al ASCO 2016) exhibiting in the high risk neoadjuvant setting a close association between lack of tumor regression following treatment with novel androgen signaling inhibitors (abiraterone +/- enzalutamide) and PTEN loss confirmed on multivariate analyses.

In the same line of questioning it becomes of interest to inquire which are the “variables” and how do they change over time and how do we track them?

Should a biomarker be ‘reflective’ of the pathway of progression rather than a ‘by association’ event? De bono et al (De Bono et al ESMO 2016) recently exhibited an association between PTEN loss and responsiveness to the combination of Abiraterone Acetate and Ipattersib not found in mCRPC tumors with PTEN intact by IHC. This is highly supportive of the need for predictive markers reflective of a pathway of progression being a more reliable approach as opposed to recent efforts focusing on markers that appear more prognostic such as for instance presence of nuclear ARV7 that may account for the failure of the ARMOR 3 galeterone trial (Bastos et al).

The new found understanding that the trials presented are only informative and in no way dismissive of the knowledge acquired preclinically and through tissue based research is integral to our progress towards precision.

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