Non-invasive interrogation of oligometastatic castration-resistant prostate cancer and the benefit of metastasis directed therapy in the phase II FORCE randomized clinical trial

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Abstract:

Metastasis Directed Therapy (MDT) is the focus of recently completed and ongoing clinical trials in prostate cancer. MDT delays the initiation of hormone therapy in biochemically recurrent prostate, but remains noncurative as >75% of patient's progress within 3 years. In castration-resistant prostate cancer (CRPC), there has been a paucity of investigation as to the benefit of MDT. The potential of MDT may be greater in oligometastatic CRPC (omCRPC), than earlier in the disease course. This is rooted in data generated from whole genome sequencing that demonstrated CRPC metastasis seed new metastasis. Additionally, the greater burden of disease, the more rapid resistance develops on next-generation hormone therapies, due to either higher intrapatient *de novo* heterogeneity and/or the probabilistic nature of a greater tumor burden and greater number of mutations developing during treatment. Thus, concurrent treatment with first line CRPC therapy (e.g. enzalutamide or abiraterone) and MDT, may significantly increase time on first line treatment by suppressing the development of resistance, while decreasing metastases to metastases spread. In parallel to the surge of interest in MDT, the field of molecular imaging is exploding. However, there is a need to understand the true "benefit" and biological significance of molecular imaging detected disease, especially in patients that already have known metastatic disease detected by conventional imaging. We are leveraging the ongoing randomized phase II FORCE (FOcal Radiation for oligometastatic Castration-rEsistant prostate cancer) trial of first line systemic therapy with or without MDT by radiotherapy based on conventional imaging (CT and bone scan), to assess the natural history of untreated PSMA positive, conventional imaging negative lesions. This trial design, combined with circulating correlative analysis (circulating tumor cells, cell free DNA), will allow us to investigate the safety and efficacy of MDT in omCRPC (Aim 1), the potential impact of PSMA positive, conventional imaging negative metastases in patients treated with first line systemic therapy (Aim 2), and to assess non-invasively resistance patterns gain or loss and the potential elimination of circulating disease (Aim 3). It is too early to have any quality conclusions from these correlative studies at this time. Ultimately, the trial will improve our molecular and radiographic understanding of omCRPC, and whether MDT has biologic/clinical benefit.

Conflicts of Interest:

Z.R.R.: No conflicts of interest to report
S.A.T.: ST has served as a consultant and received honoraria from Roche/Ventana Medical Systems, Almac Diagnostics, Janssen, AbbVie and Astellas/Medivation; he is also a co-founder and employee of Strata Oncology.
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