Interim results from a phase II randomized trial of Observation versus stereotactic ablative RadiatIon for OLigometastatic prostate CancEr (ORIOLE)

Tran PT, Radwan N, Phillips R, Ross A, Rowe SP, Gorin MA, Antonarakis ES, Deville C, Greco S, Denmeade S, Paller C, Song DY, Diehn M, Wang H, Carducci M, Pienta KJ, Pomper MG, DeWeese TL, Dicker A, Eisenberger M

Depts of Radiation Oncology, Radiology, Urology, and Medical Oncology, Johns Hopkins Medicine, Baltimore, MD

Background: Local ablative treatment to oligometastatic patients can result in long term disease-free survival in colorectal and sarcoma patients. The importance of consolidating all macroscopic tumor deposits in prostate cancer in the modern era is an unanswered question. Stereotactic ablative radiation (SABR) is highly focused, high-dose radiation that is ideally suited for treatment of oligometastatic patients. There are also exciting animal and patient studies suggesting that SABR can activate the immune system against cancer cells. Here we report on interim safety, clinical and translational outcomes of our Phase II randomized trial of SABR to men with recurrent low volume (1-3 metastases) hormone sensitive metastatic prostate cancer.

Methods: Patients are randomized 2:1 to SABR:observation with minimization to balance assignment by primary intervention, prior hormonal therapy, and PSA doubling time. Progression after 6 months will be compared using Fisher's exact test. Hazard ratios and Kaplan-Meier estimates of progression free survival (PFS), ADT free survival (ADT-FS), time to locoregional progression (TTLP) and time to distant progression (TTDP) will be calculated based on an intention-to-treat. Local control will be assessed using RECIST 1.1 criteria. Adverse events will be summarized by type and grade. Quality of life pre- and post-SABR will be measured by Brief Pain Inventory. Further fundamental analysis of the oligometastatic state with be achieved through correlation with germline DNA repair gene mutations using the Color Genomics panel, investigational ^{18}F-DCFPyL PET/CT imaging and measurement of circulating tumor cells, circulating tumor DNA and circulating T-cell receptor repertoires.

Results: Since activation in April 2016 we have had enrollment of 35 men and subsequent randomization of 34 out of the target 54 men. Thus far, as expected only minimal side-effects (no $\geq$Grade 3 toxicity) have been observed from the SABR alone. 71% (5/7) of eligible men on the observation arm have progressed at 6-months versus 33% (4/12) for the SABR arm. Of the five men tested none had germline DNA repair gene mutations. CellSearch™ detected only 1 CTC/7.5-ml in two men and the remaining eight men had no CTCs (20% detectability). In contrast, 9/17 (53% detectability) men had detectable CTCs using the HD-CTC platform and 3/4 (75%) interpretable cases showed a response following SABR. Other radiologic and blood correlatives are pending analysis.

Conclusions: The ORIOLE trial (NCT02680587) is the first randomized Phase II study in the Western Hemisphere evaluating the safety and efficacy of SABR in oligometastatic hormone-sensitive prostate cancer. Preliminary clinical data is promising and leading-edge laboratory and imaging correlates will allow an unprecedented opportunity to characterize, in isolation, the effects of SABR on the dynamics of and immunologic response of the oligometastatic state.

Conflict of Interest: The authors declare no conflicts.

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