Addition of Metastasis-Directed Therapy to Intermittent Hormone Therapy for Oligometastatic Prostate Cancer The EXTEND Phase 2 Randomized Clinical Trial

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Abstract

Importance: Despite evidence demonstrating an overall survival benefit with up-front hormone therapy in addition to established synergy between hormone therapy and radiation, the addition of metastasis-directed therapy (MDT) to hormone therapy for oligometastatic prostate cancer, to date, has not been evaluated in a randomized clinical trial.

Objective: To determine in men with oligometastatic prostate cancer whether the addition of MDT to intermittent hormone therapy improves oncologic outcomes and preserves time with eugonadal testosterone compared with intermittent hormone therapy alone.

Design, setting, participants: The External Beam Radiation to Eliminate Nominal Metastatic Disease (EXTEND) trial is a phase 2, basket randomized clinical trial for multiple solid tumors testing the addition of MDT to standard-of-care systemic therapy. Men aged 18 years or older with oligometastatic prostate cancer who had 5 or fewer metastases and were treated with hormone therapy for 2 or more months were enrolled to the prostate intermittent hormone therapy basket at multicenter tertiary cancer centers from September 2018 to November 2020. The cutoff date for the primary analysis was January 7, 2022.

Interventions: Patients were randomized 1:1 to MDT, consisting of definitive radiation therapy to all sites of disease and intermittent hormone therapy (combined therapy arm; n = 43) or to hormone therapy only (n = 44). A planned break in hormone therapy

occurred 6 months after enrollment, after which hormone therapy was withheld until progression.

Main outcomes and measures: The primary end point was disease progression, defined as death or radiographic, clinical, or biochemical progression. A key predefined secondary end point was eugonadal progression-free survival (PFS), defined as the time from achieving a eugonadal testosterone level (≥150 ng/dL; to convert to nanomoles per liter, multiply by 0.0347) until progression. Exploratory measures included quality of life and systemic immune evaluation using flow cytometry and T-cell receptor sequencing.

Results: The study included 87 men (median age, 67 years [IQR, 63-72 years]). Median follow-up was 22.0 months (range, 11.6-39.2 months). Progression-free survival was improved in the combined therapy arm (median not reached) compared with the hormone therapy only arm (median, 15.8 months; 95% CI, 13.6-21.2 months) (hazard ratio, 0.25; 95% CI, 0.12-0.55; P < .001). Eugonadal PFS was also improved with MDT (median not reached) compared with the hormone therapy only (6.1 months; 95% CI, 3.7 months to not estimable) (hazard ratio, 0.32; 95% CI, 0.11-0.91; P = .03). Flow cytometry and T-cell receptor sequencing demonstrated increased markers of T-cell activation, proliferation, and clonal expansion limited to the combined therapy arm.

Conclusions and relevance: In this randomized clinical trial, PFS and eugonadal PFS were significantly improved with combination treatment compared with hormone treatment only in men with oligometastatic prostate cancer. Combination of MDT with intermittent hormone therapy may allow for excellent disease control while facilitating prolonged eugonadal testosterone intervals.