


Intensification of Androgen Deprivation Therapy in High-Risk, Nonmetastatic Prostate Cancer: Lessons From STAMPEDE

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In this issue of the Journal, James et al. (1) present the long-term survival outcomes from the STAMPEDE phase III randomized controlled trial investigating the addition of docetaxel to long-term hormone therapy for high-risk, nonmetastatic (M0) prostate cancer. Of note, the first practice-changing STAMPEDE publication included M0 and M1 prostate cancer subjects and demonstrated that the addition of upfront docetaxel to standard-of-care (SOC) therapy including androgen-deprivation therapy (ADT) conferred an overall survival (OS) benefit in patients with locally advanced and metastatic castration-sensitive prostate cancer over SOC (control) alone (2). The long-term survival results of the M1 STAMPEDE cohort for upfront docetaxel have been previously reported and showed that the addition of docetaxel to SOC demonstrated an OS benefit over SOC alone (hazard ratio [HR] = 0.81, 95% confidence interval [CI] = 0.69 to 0.95; $P = .009$) in the first-line treatment of metastatic castration-sensitive prostate cancer (3). The STAMPEDE Trial Management Group now separately report the long-term results from the nonmetastatic prostate cancer cohort of docetaxel addition to SOC.

Using STAMPEDE's multi-arm multistage platform design to compare treatments against SOC, patients with newly diagnosed prostate cancer or high risk of relapse after previous radical treatment without prior long-term ADT were eligible and enrolled for this docetaxel comparison from 119 sites in the United Kingdom and Switzerland between October 5, 2005, and March 31, 2013 (1). Eligible patients were randomly assigned (2:1) to receive the control of long-term ADT (SOC) or experimental therapy with the addition of 6 cycles of docetaxel (75 mg/cm²) every 3 weeks plus 10 mg prednisolone daily to SOC ADT. Before November 14, 2011, SOC could include prostate radiotherapy irrespective of nodal status, which was optional but encouraged. After November 14, 2014, SOC radiotherapy was mandated for patients with node-negative (N0) disease and encouraged for node-positive disease. The primary endpoint of the study was metastatic progression-free survival (mPFS,

defined as the time from random assignment to new metastatic disease or death from prostate cancer), which has been shown to be a surrogate measure for OS in M0 patient cohorts.

With a median duration of follow-up of 81.2 months, 690 nonmetastatic patients recruited to the study reported by James et al. (1): 460 patients to the control group and 230 patients to the docetaxel group. Baseline patient characteristics were well balanced across control and docetaxel groups. The addition of docetaxel did not statistically significantly improve mPFS over control (HR = 0.89, 95% CI = 0.66 to 1.19; stratified log-rank test $P = .43$) with a 5-year mPFS rate of 82% (95% CI = 78% to 87%) for the docetaxel group (docetaxel plus SOC) vs 77% (95% CI = 73% to 81%) for the control group (SOC). The addition of docetaxel to SOC did improve failure-free survival (HR = 0.70, 95% CI = 0.55 to 0.88; $P = .002$) and progression-free survival (PFS) with an increase in restricted mean survival time over of 5.8 months (95% CI = 1.2 to 10.5; $P = .015$) over SOC (control). However, the addition of docetaxel to SOC did not statistically significantly improve OS (HR = 0.88, 95% CI = 0.64 to 1.21; $P = .44$) or prostate cancer-specific survival (sub-HR = 0.84, 95% CI = 0.58 to 1.23; $P = .37$) over SOC (control). The 5-year OS rates were 81% (95% CI = 77% to 85%) and 87% (95% CI = 82% to 91%) for the control and docetaxel groups, respectively. In short, the addition of docetaxel to SOC ADT improved failure-free survival and PFS over SOC alone in patients with high-risk, M0 prostate cancer, but this failed to translate into meaningful improvements in key long-term efficacy outcomes of mPFS, OS, or prostate cancer-specific survival.

In attempting to explain why this iteration of the STAMPEDE trial failed to meet the primary endpoint of mPFS and key secondary endpoints of OS and prostate cancer-specific survival with the addition of docetaxel to SOC in high-risk, M0 prostate cancer, it would be prudent to place it in the context of another STAMPEDE trial analysis that was positive for its primary endpoint in high-risk, M0 prostate cancer (4). Using the STAMPEDE multi-arm multistage platform, this separate study analyzed 2

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randomized controlled, open-label phase III trials randomly assigning high-risk, M0 prostate cancer patients (1:1) to SOC ADT with abiraterone and prednisolone vs SOC (control) or SOC ADT with abiraterone, prednisolone, and enzalutamide vs SOC (control) in the second trial (4). Control groups were nonoverlapping across both phase III trials, and SOC was recommended to be 3 years of ADT with radiotherapy being similarly mandated for patients with N0 disease and encouraged for node-positive disease. Abiraterone acetate (1000 mg) with prednisolone alone or with enzalutamide (160 mg) were given orally once daily for 2 years or until disease progression. The primary endpoint of this meta-analysis was metastasis-free survival, defined as time from randomization to death from any cause or to distant metastases confirmed by imaging.

From November 15, 2011, to March 31, 2016, 1974 nonmetastatic prostate cancer patients were randomly assigned to both trials (455 to control [SOC] vs 459 to abiraterone plus SOC and 533 to control vs 527 to abiraterone plus enzalutamide plus SOC trial) (4). With a median follow-up of 72 months (interquartile range [IQR] = 60-84), metastasis-free survival was statistically significantly longer in the combination groups (combined analysis of abiraterone plus SOC and abiraterone plus enzalutamide plus SOC) than in the control groups (median not reached, IQR not evaluable vs median not reached; IQR = 97 to not evaluable, HR = 0.53, 95% CI = 0.44 to 0.64; $P < .0001$). The 6-year metastasis-free survival was 82% (95% CI = 79% to 85%) and 69% (95% CI = 66% to 72%) in combination groups vs the control groups, respectively. Notably, there was no statistically significant difference in metastasis-free survival with the combination of enzalutamide and abiraterone vs abiraterone alone (interaction HR = 1.02, 95% CI = 0.70 to 1.50; $P = .91$) and no evidence of between-trial heterogeneity ($I^2 P = .90$). Similarly, the combination groups showed statistically significantly longer OS (HR = 0.60, 95% CI = 0.48 to 0.73; $P < .0001$), prostate cancer-specific survival (HR = 0.49, 95% CI = 0.37 to 0.65; $P < .0001$), and PFS (HR = 0.44, 95% CI = 0.36 to 0.54; $P < .0001$) than the control groups.

The beauty in comparing the STAMPEDE analyses by James et al. (1) and Attard et al. (4) is that both used the same European sites and enrolled a nearly identical population of patients with high-risk, M0 prostate cancer under the STAMPEDE study design. Both studies enrolled participants with a median age of older than 65 years (65 years for control vs 66 years for docetaxel and 69 years for control vs 68 years for combination abiraterone and enzalutamide), enrolled a majority of N0 disease (61% for control vs 61% for docetaxel and 61% for control vs 62% for combination group), enrolled a majority of Gleason score 8-10 (72% for control vs 80% for docetaxel and 82% for control vs 81% for combination group), and enrolled a majority of T3-T4 disease (87% for control vs 94% for docetaxel and 93% for control vs 94% for combination group). Although both studies enrolled a majority of those planned for radiotherapy to SOC ADT, there was a higher use of SOC radiotherapy (88% for control vs 89% combination group) in the abiraterone and enzalutamide trials compared with the current trial (63% for control vs 60% docetaxel), whereas the median prostate-specific antigen was slightly higher in the current study (42 ng/mL for control vs 44 ng/mL for docetaxel) than the abiraterone and enzalutamide trials (34 ng/mL for control vs 32 ng/mL for combination group). In either case, however, the percentages were balanced within the respective studies.

With limitations in cross-trial comparisons being noted, it is nonetheless difficult to solely ascribe the different results from both studies to differences in study population as both accrued

a similar patient population based on similar high-risk M0 criteria under the same STAMPEDE design (1,4). However, a key difference between the 2 studies is in the sample size whereby the abiraterone and enzalutamide studies enrolled a 1974 M0 patients, and the docetaxel comparison enrolled 690 M0 patients. The docetaxel plus SOC arm enrolled 230 patients because of the 2:1 randomization, whereas the abiraterone plus SOC arm enrolled more than double that with 533 patients. Of note, analysis showed a strong effect separately for abiraterone alone plus SOC for metastasis-free survival over control (SOC) (HR = 0.54, 95% CI = 0.43 to 0.68; $P < .0001$) (4). It is therefore likely that the docetaxel comparison in high-risk, M0 prostate cancer was underpowered to detect a clinically meaningful benefit in mPFS over control with the addition of docetaxel to SOC.

However, beyond the issue of an adequately powered study, the results of James et al. (1) are consistent with other phase III studies showing that the addition of docetaxel to SOC in high-risk, M0 prostate cancer delays relapse-free survival, but it does not confer a benefit to metastasis-free or OS (5,6). The constellation of these findings therefore paint a bigger picture that dampens the enthusiasm for the role of docetaxel in the high-risk, M0 prostate cancer space. As the authors of this study rightfully state, upfront chemotherapy should be avoided for patients planned for radical radiotherapy. Instead, it should be advocated that the addition of abiraterone to SOC should be the new standard for high-risk, M0 prostate cancer. Although an indirect comparison cannot exclude a small benefit from the combination of enzalutamide and abiraterone to SOC, the addition of enzalutamide and abiraterone to SOC is not justified because of increased toxicity and cost with this approach.

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