

# Prostate Cancer: Summary from ASCO 2015

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## STAMPEDE: Docetaxel, Zoledronic Acid, or the Combination in Advanced Prostate Cancer

The STAMPEDE study was presented at American Society of Clinical Oncology (ASCO) 2015; this study comprised 2962 men with high-risk locally advanced or metastatic prostate cancer, all starting long-term hormone therapy (HT) for the first time.<sup>1</sup> The overall study included evaluations of several different therapies added to HT. This particular presentation focused on the HT groups adding docetaxel, zoledronic acid, or both. The primary efficacy endpoint was overall survival (OS).

The most compelling finding from this analysis was that there was a highly significant OS and failure-free survival (FFS) advantage to adding docetaxel to the HT standard of care for locally advanced, non-metastatic prostate cancer. For FFS, the median was 37 months for HT plus docetaxel and 21 months for HT alone (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.54–0.7,  $p < 0.0001$ ). For OS, there was also a significant advantage (Fig. 1). The median OS was 77 months for the HT plus docetaxel arm and 67 months for HT alone (HR 0.76, 95% CI 0.63 to 0.91;  $p = 0.003$ ).

There was no significant difference in FFS or OS between the HT arm and the HT plus zoledronic acid arm, and the combination of HT plus docetaxel plus zoledronic acid produced survival results similar to HT plus docetaxel. Analysis of safety did not reveal any signals beyond those that might be expected for the individual therapies involved.

The STAMPEDE study suggests, based upon its compelling data, that docetaxel should be considered for select men with high-risk, non-metastatic disease.

Docetaxel has also been evaluated in addition to HT among men with castration sensitive prostate cancer with biochemical recurrence following radical prostatectomy (RP).<sup>2</sup> In a study presented at ASCO 2015 involving 413 patients, the authors showed that docetaxel in this setting was associated with only a marginal benefit, with a non-significant improvement in progression-free survival (PFS).

## GETUG AFU 16

One study that did have significant findings in the post-RP setting was the GETUG AFU 16, which assessed the efficacy of radiotherapy (RT) alone versus RT plus HT on PFS among men with biochemical recurrence after RP.<sup>3</sup> There was a statistically significant benefit in PFS in favour of RT plus HT, with five-year PFS rates of 79.6% for the combined approach and 62.1% for HT alone (HR 0.50, 95% CI 0.38–0.66). There was no significant difference in OS to date.

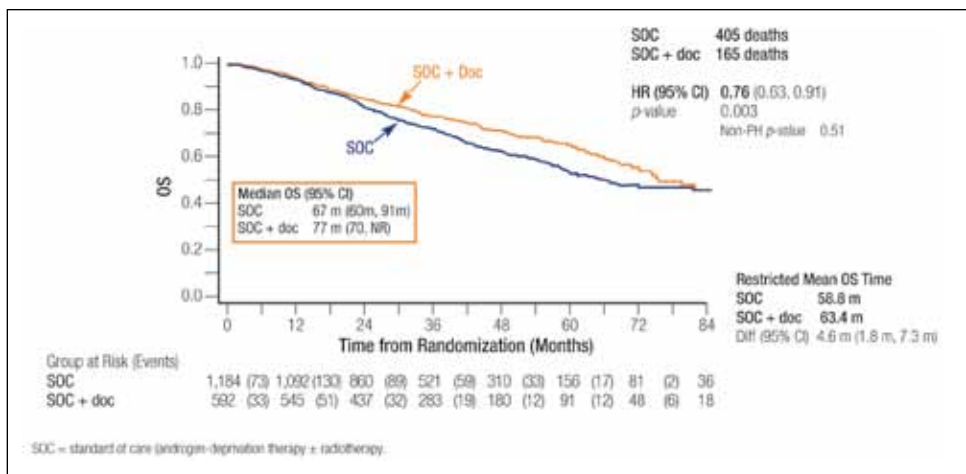
## RTOG 0521

The *Phase III Protocol of Androgen Suppression (AS) and 3DCTR/IMRT Vs AS and 3DCTR/IMRT Followed by Chemotherapy With Docetaxel and Prednisone for Localized, High-Risk, Prostate Cancer* (RTOG 0521) trial<sup>4</sup> randomized 562 men with high-risk localized prostate cancer treated with radiation and two years of androgen deprivation therapy (ADT), with and without the addition of adjuvant docetaxel (six cycles) and prednisone starting four weeks after radiation. The four-year OS was 93% for the docetaxel arm versus 89% in the standard group ( $p = 0.04$ , HR 0.70). The five-year disease-free survival (DFS) was 73% for the docetaxel arm compared to 66% for non-docetaxel arm, suggesting a benefit for those patients having radiation for high-risk non-metastatic disease with the addition of two years ADT and adjuvant docetaxel.

## Radium-223: New Data on Timing and Patient Selection

There was a substantial number of presentations and posters dealing with the use of radium-223 in advanced prostate cancer.

Several of these reports came from the radium-223 early access program (EAP) in the United States.<sup>14-16</sup> This program had two major objectives: to provide access to radium-223 for patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases; and to assess acute and long-term safety in a real-world setting.<sup>5</sup> Prior reports have shown that radium-223 is well tolerated in this setting, with no new safety concerns. It demonstrated a median OS of 17 months; comparatively, median OS in the *Double-blind, Randomised, Multiple Dose, Phase III, Multicentre Study of Alpharadin in the*



**Fig. 1.** OS with Hormone Therapy ± Docetaxel in Advanced Prostate Cancer (STAMPEDE). OS: overall survival; SOC: doc; HR: hazard ratio; CI: confidence interval; NR: not recorded; SOC: standard of care (androgen deprivation therapy ± radiotherapy; doc: docetaxel.

*Treatment of Patients With Symptomatic Hormone Refractory Prostate Cancer With Skeletal Metastases (ALSYMPCA)* study was 14.9 months for the radium-223 arm versus 11.3 months for placebo.<sup>6</sup>

There have also been several other analyses performed using this data set. Among the findings presented at ASCO 2015 was the observation of pain scores during radium-223 treatment.<sup>5</sup> Among patients not on opioids at baseline, radium-223 was associated with meaningful pain relief in 43% of patients, while 19% had no change from baseline, 28% had worse pain during treatment, and 10% experienced a mix of improved pain and worsening pain.<sup>5</sup>

Another observation from the US EAP database was that patients who had previously received treatment with abiraterone or enzalutamide were less likely to complete more than four cycles of radium-223 (36% completed more than four cycles) compared to those who had not been previously treated with abiraterone or enzalutamide (62% completed more than four cycles).<sup>7</sup> It is unclear, however, if these fewer cycles affects the overall efficacy of radium-223.

In a separate EAP involving radium-223-treated patients in the rest of the world outside the US, researchers observed that OS is longer among those patients also treated with concomitant denosumab or abiraterone than among those who did not receive these therapies while receiving radium-223 treatment.<sup>8</sup> This intriguing finding regarding combination therapy in this single arm study merits further investigation.

Overall, the data from the radium-223 EAPs show that the agent is well tolerated, with no new safety concerns and an OS similar to the pivotal Phase III study.<sup>5-8</sup> Outcomes in certain specific subgroups suggest greater benefit with earlier use of radium-223.<sup>6,7</sup>

Other data published in conjunction with ASCO 2015 showed that, over three years following the ALSYMPCA study,

radium-223 was not associated with any new safety concerns or secondary malignancies.<sup>9</sup>

Data from a Phase I/II study showed that radium-223, in combination with docetaxel among men with CRPC and bone metastases, was associated with more favorable changes in prostate-specific antigen (PSA) and bone-specific alkaline phosphatase (bALP; a marker of bone formation).<sup>10</sup> It is known from previous that those patients with lower serum alkaline phosphatase (<220 U/L) at baseline had less significant OS, but did not have a significant delay in time to symptomatic skeletal event (SSE; 16.5 vs. 10.2 months).

Finally, two other posters at ASCO 2015 showed the design of ongoing studies evaluating radium-223. The *Phase III Randomized, Double-blind, Placebo-controlled Trial of Radium-223 Dichloride in Combination With Abiraterone Acetate and Prednisone/Prednisolone in the Treatment of Asymptomatic or Mildly Symptomatic Chemotherapy-naïve Subjects With Bone Predominant Metastatic Castration-resistant Prostate Cancer (ERA223)*, investigating radium-223 in combination with abiraterone acetate and prednisone among chemotherapy-naïve men with CRPC and bone metastases, is currently recruiting patients.<sup>11</sup> A separate Phase II study is comparing the use of sipuleucel-T alone with sipuleucel-T plus radium-223 in CRPC patients with bone metastases but no visceral involvement.<sup>12</sup> In *post hoc* analyses, OS was longer in patients who had no pain versus mild-moderate versus severe; had ECOG PS of 0–1 versus ECOG PS ≥2; and had ALP levels of <220 U/L versus ≥220 U/L.<sup>12</sup>

## ODM-201

Another therapy currently undergoing investigation in non-metastatic CRPC is ODM-201, a novel second-generation oral androgen receptor inhibitor. The design of the *Multinational*,

*Randomised, Double-blind, Placebo-controlled, Phase III Efficacy and Safety Study Of ODM-201 in Men With High-risk Non-metastatic Castration-resistant Prostate Cancer (ARAMIS)* study was presented at ASCO 2015.<sup>13</sup> This trial is currently recruiting and is expected to enrol approximately 1,500 patients on HT; patients will be randomized ODM-201 600 mg or placebo twice daily. The primary endpoint is metastasis-free survival.

## Optimizing ADT

Several studies presented at ASCO 2015 evaluated ways to optimized ADT for patient with prostate cancer.<sup>14-16</sup> One such study showed that intermittent ADT was not useful for reducing the incidence of side effects over the long term compared to continuous ADT in metastatic prostate cancer.<sup>14</sup> In fact, those men who were on intermittent therapy had a slightly increased incidence of ischemic and thrombotic events compared to those on continuous therapy.

With respect to initiation of ADT, the *TROG 03.06 and VCOG PR 01-03: The Timing Of Androgen Deprivation Therapy In Prostate Cancer Patients With A Rising PSA (TOAD) Collaborative Randomised Phase III Trial* examined 293 patients with PSA relapse after definitive therapy to compare if immediate ADT versus delayed ADT affected OS. Unfortunately, this trial did not meet its target accrual of 750 patients; however, this study did show that the 142 men who had immediately initiated ADT had numerically, but not significantly, better OS, lower risks of all-cause mortality, prostate cancer-related mortality, and death from other causes compared to those 151 men whose ADT therapy was delayed.<sup>15</sup>

Finally, a prospective study of ADT therapy based on serial testosterone levels (measured every six weeks among patients who had been on fixed-schedule injections of a LHRH agonist) showed that the testosterone-guided approach was associated with a substantial reduction in exposure to, costs of, and symptoms from ADT, while castrate levels of testosterone were maintained.<sup>16</sup>

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