



The STAMPEDE trial: paradigm-changing data through innovative trial design

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Comment on: James ND, Sydes MR, Clarke NW, *et al.* Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163-77.

Abstract: Despite the numerous regulatory approvals for prostate cancer, metastatic prostate cancer remains a huge burden for men worldwide. In an exciting development, James *et al.* recently published data from the Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: a multi-stage multi-arm randomised control trial (STAMPEDE). This is an innovative multi-arm multi-stage (MAMS) trial that has utilized one control arm and several comparator arms in order to provide evidence for the inclusion of therapies beyond standard androgen deprivation alone. The patient population included: (I) men with high-risk, non-metastatic, node-negative disease; (II) men with distant-metastatic or node-positive disease; and (III) men with previously-treated prostate cancer by prostatectomy or definitive radiotherapy presenting with relapse. Men were to continue androgen deprivation for at least 2 years. The current data published by this group supports earlier results and provides additional evidence that docetaxel utilized in an up-front fashion provides a survival benefit in men with hormone-sensitive metastatic prostate cancer. Moreover, the initial results from STAMPEDE show how therapies without a demonstrated survival benefit can be efficiently excluded from further study once the likelihood of a benefit is ruled out by a predetermined analysis. In this piece, we will review the STAMPEDE data, contrast it with existing results, and provide our perspectives on how this will affect future trial conduct in the field of prostate cancer.

Keywords: Androgen deprivation; docetaxel; stampede; zoledronic acid

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The problem with standard trial development

Many therapies have been in development for the treatment of recurrent/metastatic prostate cancer, but the approval process has been slow (1). This delay in approvals can lead to high cost of drug development and clinical trials required to ensure safety and efficacy. Moreover, the most commonly used trial process, whereby positive phase II data lead to phase III trial development, is not always predictive of ultimate success in phase III. There are several examples of encouraging phase II results that did not translate to anticipated positive phase III results in prostate cancer trials (2), including data from combining docetaxel with the agents dasatinib (3), lenalidomide (4), calcitriol (5),

bevacizumab (6) and more recently using cabozantinib monotherapy (7).

There are several possible ways to overcome these hurdles, such that resources are not spent on large ineffective trials. One way has been to design randomized phase II trials with the power to detect more-than-modest effects. Investigators have also been more aggressive with presentation of phase II data for regulatory approval. Lastly, groups have foregone phase II trials and moved to phase III trials based on early phase I data, but this may add to the risk of a negative phase III trial. Despite these strategies, there is general agreement that the multitude of large-scale trials needed to test various agents and combinations has been time-consuming, inefficient and cost-prohibitive.

Multi-arm multi-strategy trial design

One promising strategy to permit the efficient and economical testing of monotherapies and combinations is the multi-arm multi-stage (MAMS) trial design used in STAMPEDE. This adaptable format utilized one control and five comparator arms that accrued simultaneously in a 2:1:1:1:1:1 ratio, in order to rapidly test agents for efficacy and safety, and to allow early termination of ineffective arms.

The STAMPEDE control arm had an initial pilot stage to assess for safety. The various interventional arms were then compared to the control arm at predetermined time-points, with multiple intermediate outcomes related to the final primary outcome. For instance, failure-free survival (FFS) served as the intermediate outcome and overall survival (OS) was the final outcome. These predetermined intermediate assessments provide early opportunities to stop ineffective treatments that did not meet early efficacy metrics. These multiple early 'hurdles' help ensure that only beneficial treatments continue to final assessments. A key feature of the MAMS format is the proper choice of an intermediate assessment endpoint. No effect on an intermediate outcome measure (null hypothesis being true) makes it likely that there would be no effect on the primary outcome measure (8-10).

STAMPEDE research arms

STAMPEDE has enrolled >7,500 men beginning first-line androgen deprivation therapy (ADT) from over 100 centers from the UK and Switzerland. Original arms included men randomized to receive either ADT alone, ADT + zoledronic acid, ADT + docetaxel, ADT + docetaxel and zoledronic acid, ADT + celecoxib, and ADT + zoledronic acid + celecoxib (9). In this perspective, we will discuss the arms detailed by James *et al.* (11) describing the effect of ADT + docetaxel (with or without zoledronic acid).

Standard hormone therapy

The control arm of STAMPEDE has provided valuable information on outcomes and prognostic factors for men in the three target populations discussed above. Between 2005 and 2014, 917 men with M1 prostate cancer were enrolled in the control group (12). In total, 62% had bone metastases only, 26% had bone and soft-tissue metastases, and 12% had soft-tissue metastases only (most involving lymph nodes). Baseline characteristics associated with worse FFS and OS included poor performance status ≥ 1 , Gleason

sum ≥ 8 , presence of bone metastases, and younger age at diagnosis. FFS for the control group was 11.2 months while OS was 42 months. Notably, OS was similar to the control population of the CHARTED trial (13).

A total of 721 men with non-metastatic disease in the control arm of STAMPEDE were also assessed with regards to overall failure free survival (11). Altogether, 60% of the reported cohort was node negative and 40% had node positive disease. Failure free survival alone was reported, as survival was better than anticipated with limited number of deaths; 2-year OS in the non-metastatic group was 96% (95% CI, 93–97%). Five-year OS was 80% (95% CI, 72–86%). Median failure free survival in this group was 63 months (26 to NR). The hazard ratio for disease failure in N+ disease patients was 2.02 (95% CI, 1.46–2.91) compared to N0 patients. Data from this control group, while limited due to small numbers, was in line with other trials of high risk patients such as the SPG-7 trial (14) and PR07-trial (15). This provided very useful information with regards to the natural history of high risk patients, both with positive and negative nodal status.

Hormone therapy plus zoledronic acid

Zoledronic acid was FDA-approved in 2002 in an attempt to decrease morbidity from bone metastases in bone-tropic diseases including prostate cancer. In STAMPEDE, 593 patients were randomized to this arm between October 2005 and March 2013. Zoledronic acid was administered over six 3-weekly cycles, then every 4 weeks for up to 2 years. Preliminary analyses for FFS at predetermined intervals failed to show an effect from zoledronic acid added to standard ADT, irrespective of docetaxel use (11). In addition, the OS hazard ratio was 0.94 (95% CI, 0.79–1.11) with no obvious benefit from Zoledronic acid in any of the subgroup analyses including those with metastatic (M1) disease. There also appeared to be no beneficial effect on skeletal-related events (SREs).

The role of zoledronic acid or other bisphosphonates in the context of advanced prostate cancer has been examined in several other trials and in an accompanying meta-analysis published at same time of the results noted above (16-19). The results of STAMPEDE (with respect to the added value of zoledronic acid) mirrored those of the earlier findings from CALGB-90202, which was also stopped early due to lack of an effect (17). In that study, zoledronic acid provided no OS benefit and no improvement in SREs when added to ADT in men with bone-metastatic hormone-

sensitive prostate cancer.

The meta-analysis examined seven randomized trials of men with M1 disease receiving bisphosphonates in addition to ADT. Although there was a very slight OS benefit in one trial using sodium clodronate (20), analyses of the other trials showed no clear evidence of benefit from the addition of zoledronic acid in this patient population (18,19). Moreover, the meta-analysis also examined 17 trials using bisphosphonates plus ADT in men with M0 disease, and survival results extracted from the four major contributing trials showed no effect of bisphosphonates on OS (16). The evidence to date from numerous trials of men with M0 or M1 prostate cancer has led to the recommendation that zoledronic acid should not be considered standard-of-care in the hormone-sensitive setting, and those arms of the STAMPEDE trial were stopped after predetermined points of analysis.

Hormone therapy plus docetaxel

A total of 592 men were accrued to the ADT + docetaxel arm of STAMPEDE, and 550 were eventually included in the safety analyses (11). Men started docetaxel a median of 2 weeks after randomization and approximately 9 weeks after beginning ADT, a timeframe similar to other trials examining ADT plus docetaxel in the context of newly-diagnosed M1 disease (13,21,22). About 77% of patients in this arm received all six planned cycles of docetaxel. Addition of docetaxel to ADT led to a 22% reduction in risk of all-cause death (HR 0.78, 95% CI, 0.66–0.93). Moreover, there was a median OS benefit of approximately 10 months over ADT alone (71 *vs.* 81 months) with the addition of docetaxel. There was also a prostate cancer-specific survival benefit (HR 0.79; 95% CI, 0.65–0.95) and a FFS benefit for the addition of docetaxel to ADT (HR 0.61; 95% CI, 0.53–0.70). However, while the benefit from the addition of docetaxel was noted for multiple subgroups including those with M1 disease, the benefit in men with non-metastatic (M0) disease was less clear (HR 0.95; 95% CI, 0.62–1.47). The M0 patients made up a smaller proportion of the enrolled patients (31/592), had less deaths at the last follow-up, and the study was probably underpowered to determine the benefit of docetaxel in this group.

The benefit of docetaxel chemotherapy in metastatic hormone-naïve men has been examined in several other trials. There have been FFS benefits in the GETUG-15 (22), CHAARTED (13), RTOG-0521 (23), GETUG-12 (24), and TAX-3501 (25) trials. These prior studies, however, showed contrasting results with regards to OS in men with metastatic hormone-naïve disease. The CHAARTED

study showed an approximate 13.6-month OS benefit with inclusion of docetaxel in men with metastatic disease, and an even larger benefit in those with high-volume disease, defined as men with >4 bone lesions with at least one located outside of the axial skeleton, or those with visceral disease (HR 0.60; 95% CI, 0.45–0.81) (13). The added benefit in the CHAARTED study of docetaxel chemotherapy in low-volume metastatic disease is less clear, and more mature data from this cohort is pending. The initial publication showed no significant difference in OS in these CHAARTED patients (HR 0.60; 95% CI, 0.32–1.13) (13). The GETUG-15 data, with a very similar low-volume disease population, also did not show a difference in OS with the inclusion of docetaxel to initial ADT (HR 1.02; 95% CI, 0.67–1.55) (22).

Notably, a meta-analysis of available data on the added value of docetaxel in M1 hormone-sensitive patients identified five randomized control trials of suitable design for inclusion in the analysis (16). This included three studies: CHAARTED (13), GETUG-15 (22), and STAMPEDE-M1 (26) whose patients represented 93% of the 3,206 men analyzed. The HR for survival in this meta-analysis was 0.77 (95% CI, 0.68–0.87) with an absolute survival improvement of about 9% at 4 years. FFS was also reduced by 36% (HR 0.64; 95% CI, 0.58–0.70) (16). The same meta-analysis examined 11 trials of docetaxel for men with M0 disease and included GETUG-12 (24), RTOG-0521 (23) and STAMPEDE-M0 trials (26). These three trials captured 53% of the 3,978 men included in the M0 cohorts, and showed no survival benefit (HR 0.87; 95% CI, 0.69–1.09), although they did suggest an improved FFS (HR 0.70; 95% CI, 0.61–0.81) that was driven by data derived from the 3 largest trials (16).

With the overall synthesis of the data, it is our opinion that docetaxel does indeed have a role for inclusion as a standard-of-care regimen in men with hormone-sensitive metastases, particularly in (but not limited to) men with large-volume disease. While all men that have hormone-sensitive metastases may not fit the strict study criteria of high-volume disease, we have extrapolated clinically to situations that present high risk of morbidity such as impending pathological fracture, bowel obstruction or spinal cord impingement. In addition, the notion of offering up-front docetaxel to all chemo-fit patients with any volume of metastatic disease (even low-volume patients) could be supported by the STAMPEDE data which did not draw a distinction between low-volume and high-volume M1 subsets. We must also remember that even the CHAARTED study was only powered to interpret the survival benefit for

the entire study population, the low-volume vs high-volume distinction actually represent a subset analysis and should not be considered in isolation (27). Another consideration is that clinical trial populations are inherently healthier, more often willing to undergo additional treatments, and more fit for such therapies. As a result, real-world data may not result in the same rate of usage and tolerance to docetaxel as with the various trials mentioned above.

In our clinical practice, we (the authors) have not routinely adopted the use of docetaxel chemotherapy for patients with locally-advanced disease, node-only disease, or PSA-only recurrence given the lack of consistent benefit across trials or meta-analyses in these patient populations. In fact, some of the data from the M0 patients is quite difficult to interpret. For example, in the ADT + docetaxel arm of STAMPEDE, men with node-negative disease showed a 42% decrease in death compared to the node-negative men who received ADT only (HR 0.58; 95% CI, 0.41–0.81) (26). Given the proven benefit of docetaxel in M1 disease, one might expect that men with node-positive disease would have an even greater benefit. However, men in the M0 group with node-positive disease who received docetaxel had less of a relative benefit (HR 0.85; 95% CI, 0.68–1.07) than the node-negative patients (26). This suggests that the numbers of patients in the relatively small subgroups may not provide enough statistical power to truly detect a consistent difference, or possibly even that the biology of locally-advanced disease may not benefit from similar interventions as in patients with distant metastases. The picture becomes even more clouded as data from the ADT + zoledronic acid + docetaxel arm (discussed below) might perhaps suggest an antagonistic effect of zoledronic acid to the benefit of docetaxel in the node-negative subgroups, in subgroups with unknown nodal status, and in patients with performance status >1 (26). This, once again, might represent an artifact of very small patient numbers in these subgroups.

Hormone therapy plus docetaxel and zoledronic acid

The STAMPEDE authors also present data on the ADT + zoledronic acid + docetaxel arm, where prespecified analysis points showed survival benefit with docetaxel. Of note, patients in this arm received greater exposure to zoledronic acid *vs.* patients receiving zoledronic acid alone (without docetaxel). Even with this increased exposure, there was no effect of zoledronic acid on FFS, OS, or even SREs in patients that received this bone-targeting agent in addition to docetaxel and ADT. Most, if not all, of the benefit in this combinatorial group was derived from the docetaxel itself (26).

FFS in the ADT + zoledronic acid + docetaxel group was improved compared to ADT alone (HR 0.62; 95% CI, 0.54–0.70). OS in the ADT + zoledronic acid + docetaxel group was 76 months, slightly less than those men that received ADT + docetaxel alone (81 months OS), raising the question of a possible negative effect of zoledronic acid to docetaxel, although this is purely speculative.

Combined data from the STAMPEDE study inclusive of all men that received docetaxel (either with or without zoledronic acid) confirmed trends seen in CHAARTED (13,21). This same trend of an OS benefit from docetaxel in M1 disease was also seen within the GETUG-15 study, although that population was not as large and the benefit did not meet predetermined statistical significance (22). Collectively, these publications have truly led to a paradigm-changing recommendation that chemotherapy-fit men with metastatic disease should receive chemotherapy within close temporal proximity to starting ADT if improving their survival is the goal. While there was a more pronounced benefit in men with high-volume disease (consisting of >4 bone lesions with one lesion outside of the axial skeleton, or visceral metastases in the CHAARTED study) (13,21), the STAMPEDE data would argue for use of early docetaxel in all chemotherapy-fit men with newly-diagnosed metastatic hormone-sensitive disease who wish to maximally extend their lifespan. Importantly, an updated analysis of the CHAARTED low-volume metastatic cohort will be presented soon, and this may clearly influence the type of patient that might receive up-front chemotherapy moving forward.

Conclusions and remaining questions

The use of the MAMS format for the STAMPEDE trial has made it possible to quickly, efficiently and safely accrue thousands of men in one multi-purpose trial instead of sequential studies of numerous agents. The strengths of the trial design include the prospective nature of the trial, the multi-center format and national adoption, the ability to add and subtract arms in an iterative fashion, and the use of approved widely-available agents. The adaptable nature allows for appropriate new arms of interest to be easily incorporated into the trial in a relatively short period of time. This is a feat that is often not possible with a new randomized trial testing each new agent against a similar standard of care.

There are limitations, however, to this particular trial format. As with any trial, caution with applicability to the real-world clinical practice bears mention. The trial participants are often healthier and younger (with less comorbidities) than those that are typically seen in the clinic.

In this particular trial, men may have been allowed to have certain therapies such as ADT for up to 6 months prior to randomization; this may have caused trial participants to enter the study in a non-uniform staggered fashion. Further, in many of the STAMPEDE arms, follow-up remains relatively short and event rates are still too low to draw definitive conclusions. Another potential hurdle is the procurement of agents from various industry partners. This concern may partially be alleviated by the fact that the comparisons of the new agents are with the standard control arm, and not necessarily comparing each novel drug against each other. Ultimately, the ability to bring agents to market more cheaply and more efficiently may very well make it more appealing to have companies ‘play together’ for the benefit of our patients.

With an increasing number of negative phase III prostate cancer trials, including the recent cabozantinib COMET-1 trial that was recently published (7), we must become better at bringing promising agents to market while also halting trials early for agents that show no evidence of preliminary activity. The MAMS trial format allows that and more. The approach has already provided useful information on the effect of early docetaxel given together with initial ADT, has elucidated the futility of zoledronic acid in men starting hormone therapy, and has set the stage to answer questions on a number of novel approaches in men with recurrent and metastatic prostate cancer.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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