

European Urology

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--Manuscript Draft--

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| Manuscript Number: | |
| Article Type: | Letter to the Editor |
| Section/Category: | Prostate Cancer (PRO) |
| Keywords: | prostate cancer; abiraterone acetate; locally advanced or localised; STAMPEDE trial |
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Should high-risk localised or locally advanced prostate cancer patients receive abiraterone acetate in addition to androgen deprivation therapy? Update on a planned analysis of the STAMPEDE trial.

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The STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy, MRC-PR08, NCT00268476) trial is a platform, multi-arm, multi-stage trial ongoing at more than 100 hospitals in the United Kingdom and Switzerland. To date, it has randomised men with advanced prostate cancer starting long-term androgen deprivation therapy (ADT, see www.stampedetrial.org) to addition of one of seven previously reported or three as yet unreported experimental treatments [1-3]. The trial cohort is approximately equally represented by men with either high-risk, localised or locally advanced (M0) or metastatic (M1) disease. In 2017, the primary results of addition of abiraterone acetate and prednisolone (AAP) reported a consistent overall survival benefit [1]. However only 21% of events had occurred in the patients with M0 disease, leading to uncertainty for the benefit of AAP in this population. The STAMPEDE platform has also conducted a separate comparison testing addition of AAP with enzalutamide, which to date remains unreported. Given the improved outcomes for M0 patients and the clinical need to determine the efficacy of intensification of androgen receptor targeting therapy for high-risk M0 patients, we have developed a pre-specified statistical analysis plan that we summarise here following approval by our trial oversight committees in January 2020.

Firstly, we will report the outcomes with AAP for M0 patients separately from M1. Between November 2011 and March 2016, 1977 M0 patients were randomised 1:1 to the addition of AAP: the first 915 patients (to January 2014) to AAP and the subsequent 1062 (from July 2014) to AAP and enzalutamide. All patients were planned for radiotherapy to the prostate and pelvic nodes (when indicated) and fixed-duration hormonal treatment. The sequential recruitment of these two groups following the same eligibility criteria and with no shared control patients allows them to be combined. Updated outcomes for the M1 patients will be reported at a later date in parallel with ongoing molecular studies. Secondly, given a recent ICE-CaP consortium analysis reported

metastatic progression free survival (mPFS) is a valid surrogate of overall survival in M0 patients [4], the primary outcome measure will include time to distant metastases confirmed by imaging or histological evidence in addition to overall survival. Although we did not report MFS previously, we have accounted for our prior 2017 report by reducing our one-sided type 1 error rate to 1.25%. For our sample size calculation, we have retained the same target hazard ratio for a treatment effect of 0.75 used in prior comparisons [1-3]. For 90% power, we require a minimum of 300 mPFS events in the control group and our projections indicate that this should be reached in mid-2021, almost ten years after the start of accrual. All analyses are stratified as described previously and additionally by AAP or AAP with enzalutamide randomisation period.

In this short communication, we have laid down in advance our plans for the final analysis of the STAMPEDE comparisons testing the addition of AAP with or without enzalutamide to standard of care for men with newly diagnosed, hormone-sensitive localised or locally advanced prostate cancer. In doing so, we aim to inform future management strategies for this group of men where decision-making is more nuanced and long-term outcomes tend to be considerably better than for men presenting with metastatic disease.

References:

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Disclosure:

The STAMPEDE trial is supported by Cancer Research UK (CRUK_A12459) and the Medical Research Council (MRC_MC_UU_12023/25) and the comparisons referred to here were supported by research grants from Janssen and Astellas. The STAMPEDE trial has also received research support from Clovis Oncology, Novartis, Pfizer, and Sanofi Aventis. Dr Attard reports receiving grants, personal fees, nonfinancial support, and speaker fees from Janssen, Astellas, and Sanofi; personal fees, nonfinancial support, and speaker fees from AstraZeneca; and personal fees from Novartis and Bayer; in addition, Dr Attard is on the Institute of Cancer Research list of rewards to discoverers for abiraterone acetate. Dr Clarke reports receiving personal speaker and advisory fees from Astellas, AstraZeneca, Ferring, and Janssen outside the submitted work and additional research grants from AstraZeneca outside the submitted work. Dr James reports receiving personal fees from Sanofi, Janssen, and Astellas during the conduct of the study. Dr James is an employee of the Institute of Cancer Research that has a commercial interest in abiraterone acetate.