Title: STAMPEDE-ing Towards Androgen Biosynthesis Inhibition for Treatment of High-Risk Hormone-Naïve Prostate Cancer: Changing the LATITUDE

Authors: Zachary Klaassen, MD^{1,2}, Declan G. Murphy, MB BCH, BaO, FRACS, FRCS Urol³⁻⁵

Affiliation:

1. Department of Surgery, Division of Urology, University Health Network, Princess Margaret Cancer Centre, Toronto, Ontario, Canada
2. Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
3. Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Australia
4. Australian Prostate Cancer Research Centre, Epworth Healthcare, Richmond, Australia
5. The Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia

Corresponding Author

Zachary Klaassen, MD

Division of Urology

University Health Network

Princess Margaret Cancer Centre

6th Floor, 700 University Ave

Toronto, Ontario, Canada

M5G 2M9

Tel: 416-946-2851

Fax: 416-946-6590

Email: zklaassen19@gmail.com

Manuscript Word Count: 1,000

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/bju.14050](https://doi.org/10.1111/bju.14050)

This article is protected by copyright. All rights reserved

Reference Count: 6

Key Words: prostate cancer, abiraterone, androgen deprivation therapy, LATITUDE, STAMPEDE, hormone-naïve

Author Manuscript

DR. ZACHARY KLAASSEN (Orcid ID : 0000-0001-7392-8916)

DR. DECLAN MURPHY (Orcid ID : 0000-0002-7500-5899)

Article type : Comment

Article Category: Comment

Since Dr. Huggins' 1941 Nobel prize winning finding that androgen deprivation therapy (ADT) effectively controls metastatic prostate cancer (PCa), 70 years passed before CHAARTED [1] and STAMPEDE [2] demonstrated that adding docetaxel to ADT prolongs survival in men with metastatic PCa. The de novo metastatic PCa global incidence is striking: 3% in the US, 6% across Europe, 4-10% in Latin America, and 60% in Asia-Pacific [3]. Historically, ADT has been standard of care, however most men progress to metastatic castration-resistant prostate cancer (mCRPC). At the recent American Society of Clinical Oncology meeting, results of two randomized controlled trials (RCTs), STAMPEDE [4] and LATITUDE [5], were presented. These RCTs assessed the utility of adding abiraterone acetate (AA) + prednisone to ADT among men with high-risk, hormone-naïve PCa. The rationale for adding AA + prednisone to ADT is: (i) the mechanism of resistance to ADT may develop early, (ii) ADT alone does not inhibit androgen synthesis by the adrenal glands or PCa cells, and (iii) AA + prednisone improves overall survival (OS) in mCRPC patients, and (iv) reduces radical prostatectomy tumor burden (pathologic complete response) in high-risk, localized PCa [6].

LATITUDE

LATITUDE [5] was conducted at 235 sites in 34 countries. Patients had newly diagnosed, metastatic hormone-naïve PCa (with at least two of: (i) Gleason ≥ 8 disease; (ii) ≥ 3 bone lesions; (iii) measurable visceral metastasis), and were randomized 1:1 to either ADT + AA (1000 mg daily) + prednisone (5 mg) (n=597) or ADT + placebo (n=602). The co-primary endpoints were OS and radiographic progression-free survival (rPFS). Over a median follow-up of 30.4 months, patients treated with ADT + AA + prednisone had a 38% risk reduction of death (HR 0.62, 95%CI 0.51-0.76). OS rates at 3 years for the ADT + AA + prednisone arm was 66%, compared to 49% in the ADT + placebo arm. This OS benefit was consistently favorable across all subgroups including ECOG 0 and 1-2, visceral metastases, Gleason ≥ 8 disease, and bone lesions >10 . There was also a 53% risk reduction of radiographic progression or death for patients treated with ADT + AA + prednisone (median 33.0 months; HR 0.47, 95%CI 0.39-0.55) compared to ADT + placebo (14.8 months).

Secondary endpoints showed statistically significant improvement for ADT + AA + prednisone, including time to: PSA progression (HR 0.30, 95%CI 0.26-0.35), pain progression (HR 0.70, 95%CI 0.58-0.83), symptomatic skeletal-related event (SRE) (HR 0.70, 95%CI 0.54-0.92), chemotherapy (HR 0.44, 95%CI 0.35-0.56), and subsequent PCa therapy (HR 0.42, 95%CI 0.35-0.50). Secondary to these results, the study was discontinued after the first interim analysis and this is the final analysis. Adverse events were comparable between the two groups.

STAMPEDE

STAMPEDE [4] is a multi-arm RCT being conducted in the UK and Switzerland to assess novel therapeutic agents in conjunction with ADT. Inclusion criteria for the AA arm included men with newly diagnosed N1M0 or M1 PCa, or any two of the following: stage T3/4, PSA ≥ 40 ng/mL, or Gleason score 8-10. Patients undergoing prior radical prostatectomy or radiotherapy were eligible if they had more than one of the following: PSA ≥ 4 ng/mL and PSADT < 6 months, PSA ≥ 20 ng/mL, N1, or M1 disease. Patients were randomized 1:1 to standard of care (SOC; ADT for ≥ 2 years, n=957) vs SOC + AA (1000 mg) + prednisone 5 mg daily (n=960). Primary outcomes were OS and failure-free survival (FFS), where failure was defined as PSA failure, local or lymph node failure, distant metastases or PCa-death. Over a median follow-up of 40 months, there was a 37% risk reduction of death (HR 0.63, 95%CI 0.52-0.76) favoring SOC + AA + prednisone. SOC + AA + prednisone also demonstrated a 71%

improvement in FFS (HR 0.29, 95%CI 0.25-0.34), decreased SREs among the entire cohort (HR 0.46, 95%CI 0.37-0.58), and specifically in the M1 cohort (HR 0.45, 95%CI 0.37-0.58). The rate of Grade 3-5 adverse events was higher in the SOC + AA prednisone arm (47% vs 33%), and were primarily cardiovascular or hepatic in nature.

INTERPRETATION & IMPLICATIONS

The most pertinent clinical comparison is to assess outcomes of the LATITUDE [5] and CHAARTED (high-volume disease) [1] treatment arms (AA vs docetaxel). With similar median OS outcomes between the ADT control arms (suggesting similar populations), the HRs for OS based on treatment are nearly identical: 0.62 (LATITUDE) vs 0.63 (CHAARTED). Similarly, the rPFS outcomes are comparable between the two trials: HR 0.47 (LATITUDE) vs 0.53 (CHAARTED). Thus, the question is whether the impact of adding AA to ADT is volume or risk dependent. Results from STAMPEDE [4] suggest similar outcomes to LATITUDE and CHAARTED, supporting AA + ADT in patients with less burden of disease.

So, what are the long-term economic ramifications for treating hormone-naïve PCa with AA + prednisone? A conservative estimate suggests a cost of \$115,000/year/patient for AA + prednisone, resulting in a crude estimate of a \$2.8 billion annual expenditure for the drug in the US alone if used in the hormone-naïve setting [7]. Although the patent for AA expired in 2016 and there are currently 13 applications to make generic AA, the patent for prednisone lasts until 2027 (\$30 billion lawsuit) [7]. Clinically, there are also unanswered questions: Can a genomic classifier be used to select patients more likely to benefit from AA or docetaxel? Can AA be added in even earlier settings? Should AA and docetaxel be combined or used sequentially? Will the mechanisms of resistance to AA be the same when used in the non-mCRPC setting? What is the optimal therapy for patients progressing on ADT + AA, compared to those progressing on ADT + docetaxel?

Given the avoidance of potential chemotherapy related side effects for an oral, long-term treatment, AA + ADT should be considered standard of care for these patients. These RCTs provide clinicians with Level-1 evidence for improving patient care in the high-risk/metastatic setting. The investigators and more importantly the patients are to be thanked and congratulated for their perseverance and willingness to participate in these practice-changing trials. It is our job

as clinicians to continue advocating the best treatment for our patients, whether this be through economic barriers in first world countries, or access to appropriate care on a global scale.

CONFLICTS OF INTEREST

None

References:

1. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med* 2015; 373: 737-46.
2. 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 randomized controlled trial. *Lancet* 2016; 387: 1163-77.
3. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic Prostate Cancer Incidence and Prostate-specific Antigen Testing: New Insights from the European Randomized Study of Screening for Prostate Cancer. *Eur Urol* 2015; 68: 885-90.
4. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. *N Engl J Med* 2017 Jun 3 [Epub ahead of print].
5. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. *N Engl J Med* 2017 Jun 4 [Epub ahead of print].
6. Taplin ME, Montgomery B, Logothetis CJ, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: Results of a randomized phase II neoadjuvant study. *J Clin Oncol* 2014; 32: 3705-15.
7. Davies BJ. Prostate Cancer Drug About to Confront Insurers with Sovaldi-Size Problem. *Forbes*. Accessed June 5, 2017. Available at: <https://www.forbes.com/sites/benjamindavies/2017/06/05/prostate-cancer-drug-about-to-confront-insurers-with-sovaldi-size-problem/#57693b8956a7>

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Klaassen, Z;Murphy, DG

Title:

STAMPEDE-ing towards androgen biosynthesis inhibition for treatment of high-risk hormone-naive prostate cancer: changing the LATITUDE

Date:

2018-01-01

Citation:

Klaassen, Z. & Murphy, D. G. (2018). STAMPEDE-ing towards androgen biosynthesis inhibition for treatment of high-risk hormone-naive prostate cancer: changing the LATITUDE. BJU INTERNATIONAL, 121 (1), pp.9-11. <https://doi.org/10.1111/bju.14050>.

Persistent Link:

<http://hdl.handle.net/11343/293764>