BJU Int 2022; **130:** 580–581 doi:10.1111/bju.15860

BJUI
BJU International

Comment

Active surveillance versus enzalutamide for low-risk prostate cancer – was it really a trial we needed?

Isabella S.C. Williams[1], Sachin Perera[1,2], Declan G. Murphy[3], Niall M. Corcoran[1,2], Damien M. Bolton[2,4] and Nathan Lawrentschuk[1,2,5]

[1]Department of Urology, Royal Melbourne Hospital, [2]Department of Surgery, University of Melbourne, Parkville, [3]Division of Cancer Surgery, Peter MacCallum Cancer Centre, [5]EJ Whitten Prostate Cancer Research Centre at Epworth, Melbourne, and [4]Department of Urology, Austin Hospital, Heidelberg, Vic., Australia

The management of low-risk prostate cancer in North America has recently seen some unexpected, surprising, and somewhat perplexing occurrences. The sudden change in the National Comprehensive Cancer Network (NCCN) guidelines last year, no longer recommending active surveillance (AS) as the 'preferred' treatment for low-risk prostate cancer, caused confusion and concern for many alarmed that such guidance could potentially increase active treatment rates in men unlikely to benefit from intervention [1]. Fortunately, this 'enlightened guidance' was subsequently reversed shortly thereafter.

This action by the NCCN was recently followed by publication of the ENACT trial (ClinicalTrials.gov Identifier: NCT02799745) with some disconcerting conclusions. This trial randomised men to AS vs treatment with enzalutamide, a relatively toxic drug generally reserved for men with metastatic disease [2]. AS, as the term suggests is intended to mitigate against overdiagnosis and limit overtreatment. Treating with a relatively toxic drug would appear to contradict these objectives.

The justification provided for undertaking this trial is noteworthy. The authors referred to the REDEEM trial (ClinicalTrials.gov Identifier: NCT00363311), which demonstrated that dutasteride, a 5α-reductase inhibitor, when used as an adjunct in men with low-risk prostate cancer undergoing AS significantly reduced the risk of progression by 38% [3]. The ENACT authors argue additional pharmacological approaches that may reduce the risks associated with disease progression and interventional treatment are needed [2]. Studies identifying better patient selection or utilising 'less radical' treatment (or less toxic pharmacological agents) would surely be a better approach in this population, given that one-third of patients on AS progress to active treatment within 5 years. Examples include recent imaging trials using prostate-specific membrane antigen positron emission tomography-CT to better target and provide more informed initial biopsy as found in the PRIMARY trial [4], or CONFIRM trial (Australian New Zealand Clinical Trials Registry [ACTRN]12621001648819 at https://www.anzctr.org.au) aiming to better select men for AS prior to confirmatory biopsy. It would seem apparent that imaging approaches sparing men pharmacological intervention are a more logical and prudent first step. Switching from relatively archaic transrectal biopsies to transperineal biopsy, which better filters men at the initial biopsy could also be considered.

This is not the first time antiandrogen monotherapy has been trialled. In 2010, Iversen et al. [5] published a combined analysis of three trials comprising 8113 patients with localised or locally advanced prostate cancer, with patients randomised to standard care plus bicalutamide or standard care plus placebo. Following a median follow-up of 9.7 years, they found no difference in overall survival between arms. In patients with localised disease undergoing watchful waiting, there was actually a survival trend favouring placebo. Bicalutamide side-effects included breast pain (73.7%) and gynaecomastia (68.8%) [5]. Given the aforementioned, it is justifiable to query the value of another antiandrogen trial for low-risk prostate cancer.

Fast forward to 2022 and the ENACT trial, with randomisation of men to AS or enzalutamide. This trial concluded that 'enzalutamide monotherapy was well-tolerated and demonstrated a significant treatment response in patients with low-risk or intermediate-risk localized prostate cancer', and that 'enzalutamide may provide an alternative treatment option for patients undergoing AS'.

Fortunately, Shore et al. [2] excluded patients with very low-risk disease. This was both sensible and appropriate; however, the number of intermediate-risk men who arguably could be the 'target audience' of such a trial was far too low.

This brings one to the power of the study. The sample size (at least 222 participants to be accrued over 1 year) was calculated based on the REDEEM trial, with an assumed study duration of 3 years with 16% loss to follow-up and a 3-year median time to progression for the AS group (0.23 rate), with an underlying hazard ratio of 0.52. In total, 227 men across 66 sites were randomised. A total of 114 men were randomised to the treatment arm, with 85 (74.6%) completing 1 year of AS, 70 (61.4%) completing 1 year of

© 2022 BJU International.
Published by John Wiley & Sons Ltd. www.bjui.org

1464410x, 2022, 5, Downloaded from https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.15860 by South African Medical Research, Wiley Online Library on [05/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

follow-up, and 58 (50.9%) completing 1 year of continued follow-up. A total of 113 men were randomised to AS, with 80 (70.8%) completing 1 year of treatment, 51 (45.1%) completing 1 year of follow-up, and 41 (36.3%) completing 1 year of continued follow-up. Overall, only 54 men (47.4%) receiving enzalutamide and 40 men (35.4%) undergoing AS completed all study periods [2]. Thus, this trial's low completion rate makes it difficult to draw any meaningful conclusions from the available data.

Unsurprisingly, ENACT found those treated with enzalutamide experienced a substantial number of side-effects including fatigue (55.4%), gynecomastia (36.6%), nipple pain (30.4%), breast tenderness (25.9%), and erectile dysfunction (17.9%). The trial reported that only just over 7% of men withdrew due to enzalutamide side-effects, which would appear an underestimation given how few men completed the follow-up period. In contrast, the only adverse events found in the AS arm was hypertension (7.1%) [2].

The declaration of limitations within the trial is muted. Frequent reference to secondary underpowered endpoints of limitations distracts from the underwhelming number of men who completed follow-up/treatment in either arm or the significant number of men who experienced side-effects in the enzalutamide arm. Despite its limitations, this study supports the view that very careful consideration should be given before enzalutamide is used for the population addressed.

The conclusion in the ENACT trial, despite the noted side-effects and the low participant completion rate, puts a responsibility on both academic and industry interests to carefully evaluate and address the implications and conclusions of this trial.

To fully critique the ENACT trial, one needs to reflect on the primary purpose of AS as promulgated by Klotz [6]. AS was predominantly intended to reduce overtreatment in men who could be safely monitored and undergo salvage treatment should they have disease progression. AS arose in the context of overdiagnosis of men with low-risk cancer; however, those with overdiagnosis could be reassured with the knowledge their low-risk cancer was being monitored, rather than being confronted with the prospect of radical treatment.

While commending the desire to continually and effectively evaluate optimal management of early stage prostate cancer including AS the presented conclusions of the ENACT study may potentially direct patients and clinicians along an additional treatment course for which there is minimal trial justification, and for which evidence to the contrary is established.

Disclosure of Interests

Isabella Williams and Sachin Perera – none. Declan Murphy – has received honoraria for advisory board and speaker activity from Janssen, Astellas, Bayer, Ipsen, Astra Zeneca, Ferring, Sanofi, Novartis and Device Technologies. Niall Corcoran – has received research funding from Janssen and Bayer, honoraria from Mundipharma, Astellas and Bayer, and paid editorial comment from research review. Damian Bolton – Clinical Advisor Boston Scientific Australia. Grant recipient: Movember, Applaud. Nathan Lawrentschuk – Robotic Proctor Device Technologies Australia, Focal therapy proctor Getz Healthcare Australia. Clinical Advisor Boston Scientific Australia. Prior unrestricted research grant Astra Zeneca 2017.

References

1 **Chen K, Murphy D, Lawrentschuk N.** Active surveillance for low-risk prostate cancer: the uphill battles and the unnecessary ones. *J Urol* 2022; 207: 265–7

2 **Shore ND, Renzulli J, Fleshner NE et al.** Active surveillance plus enzalutamide monotherapy vs active surveillance alone in patients with low-risk or intermediate-risk localized prostate cancer. The ENACT randomized clinical trial. *JAMA Oncol* 2022: e221641. https://doi.org/10.1001/jamaoncol.2022.1641

3 **Fleshner NE, Lucia MS, Egerdie B et al.** Dutasteride in localised prostate cancer management: the REDEEM randomised, doubleblind, placebo-controlled trial. *Lancet* 2012; 379: 1103–11

4 **Emmett L, Buteau J, Papa N et al.** The additive diagnostic value of prostate-specific membrane antigen positron emission tomography computed tomography to multiparametric magnetic resonance imaging triage in the diagnosis of prostate cancer (PRIMARY): a prospective multicentre study. *Eur Urol* 2021; 80: 682–9

5 **Iversen P, McLeod DG, See WA et al.** Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. *BJU Int* 2010; 105: 1074–81

6 **Klotz L.** Active surveillance with selective delayed intervention is the way to manage 'good-risk' prostate cancer. *Nat Clin Pract Urol* 2005; 2: 136–42

Correspondence: Isabella Williams, Royal Melbourne Hospital, 300 Grattan St, Parkville, Vic., Australia.

e-mail: isabella.williams@mh.org.au

Abbreviations: AS, active surveillance; NCCN, National Comprehensive Cancer Network.

1464410x, 2022, 5, Downloaded from https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.15860 by South African Medical Research, Wiley Online Library on [05/11/2022]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License