We declare no competing interests.

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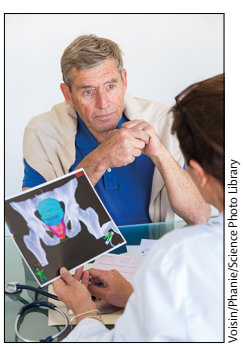
Effective and well tolerated: where do these drugs fit now?

In *The Lancet Oncology*, Bertrand Tombal and colleagues[1] describe the health-related quality of life (HRQOL) reported by participants in the PROSPER study, the main endpoints of which were published by Hussain and colleagues in 2018.[2] The trial identified a significant improvement in metastasis-free survival for men with non-metastatic, but castrate-resistant, prostate cancer who received enzalutamide in addition to standard androgen deprivation therapy, compared with those who received placebo. However, particularly for interventions designed to improve survival rather than achieve cure, there is a major trade-off that patients have to consider. What is the balance between improved survival versus extra toxicity or loss of HRQOL that the additional therapy can cause?

It is reassuring that the findings of Tombal and colleagues show no major detriment to HRQOL for men in the active treatment group. Although side-effects of androgen deprivation therapy can be severe for some individuals, this study—similar to our trial[3] investigating the effects of androgen deprivation therapy on HRQOL in men with non-curable prostate cancer—shows that castration status in the presence of relapsed or metastatic disease is compatible with a similar HRQOL to that of the equivalent general population. Whether this finding relates to psychological benefits of active intervention or good symptom control, which counterbalance any physical or psychological detriment of advanced disease, is a moot point. In the study by Tombal and colleagues, high HRQOL was maintained for roughly 2 years, which might well be attributed to slowing progression to bulky disease. Regarding specific HRQOL domains, enzalutamide increased time to deterioration in the pain severity composite index (from the Brief Pain Inventory Short Form) and in urinary symptoms (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire PR25). The Functional Assessment of Cancer therapy–Prostate (FACT-P) scale also showed longer time to deterioration in emotional wellbeing, the prostate cancer subscale, and the FACT-P total score. A longer time to deterioration of symptoms, associated with a delay in development of local or metastatic disease, is an important contributor to maintaining better functional status and overall HRQOL.

Although all men continued taking standard androgen deprivation therapy in this study, the addition of enzalutamide led to increased hormone-therapy related symptoms, which is possibly consistent with the different anti-androgen mechanism of the drug. However, the difference was not clinically significant between the groups in PROSPER. Although the incidence of grade 3 adverse events reported in PROSPER[2] was relatively high (31% enzalutamide *vs* 23% placebo), this did not appear to translate to a detriment in HRQOL.

The crucial question now is at which stage and in what sequence this drug, and others in its class (such as apalutamide, which has very similar outcomes in this patient cohort,[4] and darolutamide [NCT02200614, which is still active]) should be used most appropriately. Patients with castration-resistant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but occult disease represent a minority of patients with relapsed prostate cancer, and with the current stage migration arising from the use of more sensitive staging techniques, such as prostate-specific membrane antigen (PSMA)-PET isotope scanning, even fewer men will fall into this category. Will funding approval based on the findings from this trial encompass men affected by this stage migration, or will a further study be required? Also, focused local treatment of oligometastases (eg, with radiation therapy) might be effective in delaying disease progression,[5] and is as well tolerated, and potentially cheaper, than systemic therapy. In more advanced metastatic disease, the benefit of using this class of drugs has been shown both before and after docetaxel chemotherapy.[6–8] How are these treatment approaches best combined to optimal effect?

Conversely, there is a question about whether this class of drugs should be introduced at the start of the disease trajectory. There is long-standing evidence that treating disease earlier rather than later, and hence treating smaller volume disease before progression to symptomatic disease, improves overall survival.[9,10] This principle underlies the use of adjuvant therapy to eliminate microscopic disease and prevent subsequent relapse. The evidence that these drugs are active in castration-resistant prostate cancer is a strong indicator that they should be tested in early disease settings. There are only two randomised trials of the use of these drugs in the adjuvant setting: a study of apalutamide (NCT02531516), with analysis expected in 2026; and a study of enzalutamide with radiotherapy in men with high-risk disease (NCT02446444), which has a primary endpoint of overall survival at 5 years and a secondary endpoint of HRQOL, with analysis expected in 2021. The latter trial includes an exemplary component not included in trials to date, but which is crucial to the appropriate use of new drugs: an analysis of incremental cost-effectiveness to manage the pressures from effective novel therapies on health-care resources.

Gillian M Duchesne
Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne 3000, VIC, Australia
gillian.duchesne@petermac.org

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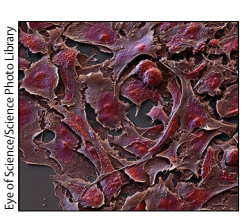
Extending the scope of PARP inhibitors in ovarian cancer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In the past decade, trials with inhibitors of oral poly (ADP-ribose) polymerase (PARP), a key enzyme involved in the repair of DNA damage, have led to a major change in the treatment of advanced ovarian cancer. A key element of the success of this class of drug is deficiency in the homologous recombination repair (HRR) pathway, which repairs DNA double-strand breaks. This deficiency is often seen in *BRCA*-mutated tumours, since functioning BRCA proteins have a major role in preserving the complex DNA repair pathway. However, other mechanisms apart from *BRCA* mutations can also result in HRR pathway alterations and consequently lead to a clinical benefit from PARP inhibitors.[1] Study of DNA damage response and manipulation of the process is now recognised as an important area of research and could lead to better cancer treatments.[2] Precise measurement of HRR is difficult, but in ovarian cancer it is most closely related to the platinum sensitivity of the