NICE guidance on enzalutamide for non-metastatic, hormone-relapsed prostate cancer

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On May 15, 2019, the National Institute for Health and Care Excellence (NICE) published guidance that did not recommend enzalutamide for the treatment of non-metastatic, hormone-relapsed prostate cancer. The committee had previously recommended enzalutamide for metastatic prostate cancer, either before chemotherapy is indicated (NICE technology appraisal guidance 377)[1] or after chemotherapy (NICE technology appraisal guidance 316).[2]

NICE appraised enzalutamide as a single technology appraisal. Astellas (Surrey, UK) submitted clinical and cost-effectiveness evidence,[3] which was critiqued by an evidence review group, the Aberdeen Health Technology Assessment Group.[4] An independent appraisal committee of health professionals, academics, lay members, and industry representatives met twice to consider the evidence and to develop the guidance on enzalutamide. Clinical and patient experts attended the first meeting; company representatives attended both meetings.

In line with the then anticipated marketing authorisation, the scope of the appraisal covered adults with non-metastatic prostate cancer that is no longer sensitive to androgen deprivation therapy (ADT), also known as hormone-relapsed or castration-resistant prostate cancer. The committee, appreciating that clinicians nonetheless continue to offer ADT to patients and which is tasked with appraising enzalutamide against established National Health Service (NHS) practice in England, considered the only relevant comparator to be ADT at this position.

The key clinical evidence came from PROSPER,[5] a blinded randomised controlled trial evaluating enzalutamide with ADT against placebo with ADT in patients with high-risk, non-metastatic, hormone-relapsed prostate cancer. High risk was defined as a serum prostate-specific antigen (PSA) concentration of 2 ng/mL or more, and a PSA doubling time of 10 months or less. The clinical experts advised that a clinically meaningful PSA doubling time in this setting would be less than 6 months, but that other factors such as age and fitness should also be considered. The committee concluded that, other than being lower risk, the population of PROSPER was similar to patients in the NHS.

The primary outcome of the trial was metastasis-free survival, which the company defined as the time to metastasis or death. In its original submission, the company presented results from the main efficacy analysis after 440 participants had metastatic disease or died. For overall survival, data originally came from an interim analysis after 165 deaths (hereafter referred to as the first analysis), corresponding to 18·5 months follow-up in the enzalutamide group; this interim analysis coincided with the main analysis of metastasis-free survival. Subsequently, the company provided, in confidence, overall survival results from a second interim analysis after 285 deaths.

In PROSPER, median metastasis-free survival was 36·6 months in the enzalutamide group and 14·7 months in the placebo group in the main analysis (hazard ratio [HR] 0·29, 95% CI 0·24–0·35; p<0·0001). The committee considered enzalutamide to be more effective than placebo at delaying metastasis.

Overall survival data from PROSPER were immature because the company planned the study to detect a statistically significant difference between treatment groups for metastasis-free survival rather than overall survival. The committee noted that the overall survival data did not show a survival benefit for enzalutamide over placebo (HR 0·80, 95% CI 0·58–1·09; p=0·152). The committee considered this result with caution because the frequency of deaths underlying the HR violated the proportional hazards assumption. Results from later data cuts were consistent with the first analysis, but remained immature, making the committee unable to judge the long-term effect of enzalutamide on survival.

The committee noted that the HRs when using enzalutamide later in the treatment pathway suggested better relative effectiveness (HR 0·76, 95% CI 0·66–0·88, for pre-chemotherapy and HR 0·62, 95% CI 0·52–0·73, for post-chemotherapy) in their respective trials compared with standard of care. The committee was aware that in the NHS, patients can take either abiraterone or enzalutamide only once in the course of disease, and the clinical experts agreed that enzalutamide appears to be less effective when used earlier in the treatment pathway.

For the cost-effectiveness analysis, the company developed an economic model, based on the treatment groups in PROSPER, comparing enzalutamide with ADT against ADT alone. The model included five mutually exclusive states: one state to represent non-metastatic disease; three states to represent the treatment pathway after non-metastatic disease; and death. The company calculated the proportions of people in each health state from data on metastasis-free survival and overall survival from PROSPER and data from other trials for later in the treatment pathway.

The model allowed death before or after metastasis, which meant that the company divided deaths from PROSPER in its model into participants who died before metastasis and those who died after metastasis. The evidence review group considered this model inappropriate because it increased the uncertainty of already immature data and also introduced a bias for patients who died after metastasis. The committee also noted that this model structure required data on metastasis-free survival, which was only available from the first analysis. Further interim analyses used to estimate overall survival would therefore not have accurate metastasis-free survival data. The committee recognised that differences in overall survival attributed to enzalutamide were the most important driver of the economic model, and concluded that it was appropriate to use the most mature data for overall survival with data on metastasis-free survival from the first analysis. The committee noted that the modelled data for overall survival from the economic model did not match what actually happened in PROSPER: that is, the observed data from the second interim analysis. The committee concluded that this discrepancy was a problem with the model structure, and its results for the proportions of participants in each health state, and the duration of treatment.

The company derived utility values in the economic model from PROSPER, which the committee concluded was the appropriate source of data for health-related quality of life. However, PROSPER showed no significant difference in quality of life between the enzalutamide and placebo groups of the trial. The company commented that enzalutamide delayed the time to deterioration of quality of life, rather than directly improving quality of life, but did not include this measurement in its economic model.

The committee was concerned that the company modelled the proportion of people who take each treatment after metastases incorrectly because the data did not match what is seen in NHS clinical practice. Notably, the company assumed that all patients who receive placebo (rather than enzalutamide) before metastatic disease receive enzalutamide after metastasis, but used data in the model from PROSPER in which a much lower number of patients received enzalutamide after metastasis. Additionally, the company did not include NHS treatment options such as cabazitaxel and radium-223 hydrochloride in its modelling.

The company estimated that the incremental cost-effectiveness ratio was £28 853 per quality-adjusted life-year gained for enzalutamide compared with ADT alone, taking into account a confidential discount. The evidence review group estimated that the incremental cost-effectiveness ratio was £56 168 per quality-adjusted life-year gained using different assumptions including using data from the second interim analysis. The committee concluded that there was substantial uncertainty around both estimates because of the immaturity of the survival data; because it had not been presented with evidence that enzalutamide prolongs life or improves quality of life; and the model's structural problems. The committee concluded that enzalutamide did not represent a cost-effective use of NHS resources and decided not to recommend enzalutamide for non-metastatic hormone-relapsed prostate cancer.

Stakeholders were given the opportunity to appeal against the committee's recommendations, but no appeals were received.

We declare no competing interests.

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Australia's election could bring down cancer costs for patients

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Cancer care in Australia is set for a major shake-up if polls prove to be right and the opposition Labor party regains power in the election on Saturday, May 18, 2019. Labor has made cancer funding central to its campaign, pledging AUS$2·3 billion (US$1·6 billion) to fund millions of free scans and free consultations plus cheaper medicines, in an attempt to reduce out-of-pocket expenses, which can run into tens of thousands of dollars per patient.

One in three Australians are estimated to be diagnosed with