Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] **registrar submitting on behalf of:**

Name of your organisation: NCRI/RCP/RCR/ACP

Comments coordinated by [redacted]

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant ***clinical guidelines*** *and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

Prostate cancer is the most commonly diagnosed cancer in men. Androgen deprivation therapy (ADT), commonly with luteinising hormone releasing hormone (LHRH) agonists, is the standard initial therapy for men with metastatic prostate cancer.1 A recent study demonstrated the median failure free survival for men who present with metastases at diagnosis was 11.2 months and median overall survival 42 months.2 When PSA or clinical progression occurs despite castrate levels of testosterone patients are said to have developed metastatic castrate resistant prostate cancer (mCRPC). Until 2010, the chemotherapy agent, docetaxel, was only systemic therapy proven to prolong overall survival in mCRPC.3 More recently large Phase III randomised controlled trials have demonstrated overall survival benefits for five further therapies as summarised below.4-9

The use of other older therapies (e.g. diethylstilboestrol, ketoconazole) or best supportive care has rapidly diminished with the availability of newer, more effective therapies. There is no proven survival benefit for these therapies. Sequencing and selection of these novel agents is a rapidly evolving and complex area. Currently, we lack stratification criteria to determine which patients may benefit from a particular agent.

NICE Technology Appraisal 101 recommends docetaxel as a treatment option for men with hormone-refractory metastatic prostate cancer, with a Karnofsky performance-status score ≥60%. This is based on phase III trial data demonstrating a survival advantage over mitoxantrone (median survival 18.9 versus 16.5 months

respectively, p=0.009).3 Approximately 50% of patients are fit enough to receive it. The treatment requires intravenous administration on a 3 weekly basis in a dedicated chemotherapy unit. Life-threatening complications including neutropenic sepsis can occur.

Abiraterone acetate, an androgen biosynthesis inhibitor, combined with prednisolone was compared to prednisolone alone in a Phase III trial in mCRPC patients who were chemotherapy-naïve.5,6 Patients with visceral metastases were not included in this study. At a median follow-up of 27.1 months the study demonstrated an improvement in radiographic progression free survival (16.5 vs 8.2 months, HR 0.52, p<0.0001) in patients treated with abiraterone.5 A pre-specified final analysis at a median of 49.2 months follow-up demonstrated an improvement in median overall survival (34.7 vs 30.3 months, HR 0.81, p<0.0033).6 A PSA reduction of ≥ 50% occurred in 62% of patients in the abiraterone group. While generally well tolerated, hypertension, cardiac disorders and abnormal liver function tests were common in the abiraterone group. Drug related adverse events led to discontinuation of treatment in 7% of patients receiving abiraterone. Abiraterone extended the time to opiate use by 10 months (33.4 months vs 23.3 months). Abiraterone has been widely used in England in chemotherapy-naïve patients through the Cancer Drugs fund. It is also approved for use in patients with mCRPC following docetaxel and, as such, there is wide-spread experience with this drug in the UK (NICE TA259). Prednisolone is required to reduce the mineralocorticoid effects of abiraterone.

Sipuleucel-T, a novel autologous active cellular immunotherapy prolonged overall survival in men with asymptomatic mCRPC not previously treated with chemotherapy (25.8 months vs 21.7 months, HR 0.78).7 Adverse events included chills, fever and headache. Sipuleucel-T requires the use of leukapherisis facilities and shipping of cells to a central European facility for processing with antigen, and then reinfusion on three occasions over a month. This treatment did not delay deterioration in quality of life. The process is therefore logistically challenging and this treatment has not been widely used in the UK to date.

The alpha-emitter radioisotope radium-223 demonstrated an overall survival benefit (14.9 vs 11.3 months, HR 0.70, p=0.002) in patients who had received, or were ineligible to receive, or declined docetaxel.8 43% of patients in this trial were chemotherapy-naive. Patients were required to have symptomatic disease with regular use of analgesic medication or palliative radiotherapy for bone pain within 12 weeks. Radium-223 is available in England but not Wales through the Cancer Drugs Fund. The patients treated in this clinical trial generally had more advanced prostate cancer as evidenced by the shorter overall survival times in both the treatment and control groups. This treatment is generally well tolerated but requires capacity in radio-isotope departments to deliver the drug intravenously.

In addition to the life extending systemic treatments described above, other options used in some UK centers for bony metastatic disease are bisphosphonates (e.g. zoledronate), the RANK ligand inhibitor denosumab and other radioisotopes (e.g. strontium-89). Radiotherapy is commonly used for metastases, particularly to bone.

Access to palliative care services is important in this patient group who are commonly frail and elderly.10 Most centers will also offer entry into clinical trials.

The major determinants for treatment decisions include: patient fitness, presence of visceral metastases, access to the Cancer Drugs Fund in England but not Wales and patient preference.

Enzalutamide is an oral second generation androgen receptor (AR) inhibitor that blocks AR binding, nuclear translocation and transcription. Enzalutamide has been approved by NICE for men with metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (TA316) and is widely used throughout the UK in this setting. In addition, it has been available for chemo-naïve patients in England via the Cancer Drugs Fund since July 2014.

The key phase III clinical trial (PREVAIL) randomly assigned 1717 patients (1:1 ratio) with chemo-naïve mCRPC to receive enzalutamide or placebo.4 The co-primary endpoints of the study were radiographic progression-free survival and overall survival. Patients with visceral metastases were eligible for the study. Previous anti-androgens and concurrent steroids were permitted. Patients were required to be ECOG performance status 0-1 and to be pain-free or mildly symptomatic (Brief Pain Inventory Short Form question 3 score </= 3). Enrolment occurred in 207 sites globally and included patients treated in the UK. 87% of patients had prior antiandrogen therapies (eg. bicalutamide) and this is likely to be consistent with use in the UK.

The independent data monitoring committee carried out an interim analysis after 540 deaths had occurred demonstrating an overall survival benefit for enzalutamide leading to early stopping of the trial. Patients from the placebo group were offered treatment with enzalutamide.

The enzalutamide group received treatment for longer (16.6 months vs 4.6 months). The median radiographic progression-free survival was not reached in the enzalutamide group and was 3.9 months in the placebo group. There was an 81% reduction in the risk of radiographic progression or death (HR 0.19, p<0.001).

The median follow-up for survival was 22 months. Treatment with enzalutamide resulted in 29% decreased risk of death (HR 0.71, p<0.001) (median 32.4 months vs 30.2 months). The median time to initiation of chemotherapy was 28 months in the enzalutamide group compared with 10.8 months in the placebo group (HR 0.35, p<0.001). Importantly, enzalutamide also prolonged median time until quality of life deterioration measured on the FACT-P scale (11.3 months vs 5.6 months, HR 0.63, p,0.001). A PSA reduction of ≥ 50% occurred in 78% of patients in the enzalutamide group. Consistent benefit was observed in all subgroups including patients with visceral disease.

More grade 3 adverse events occurred with enzalutamide (43% vs 37%) but the median time to adverse event occurrence was longer in the enzalutamide group (22.3 months vs 13.3 months). The most commonly increased adverse events were

fatigue, arthralgia, hot flushes, hypertension, falls and acute coronary syndromes. The number of patients that discontinued treatment due to adverse events was 5.6% in the enzalutamide and 6% in the control group.

Enzalutamide is used in secondary or tertiary care oncology centres by clinical and medical oncologists with specialist interest in systemic therapy for prostate cancer. It is likely that the use of enzalutamide would be within its licenced indication and this appraisals scope. Additional care includes trained nurses and pharmacists to supply the drugs and manage/monitor patients at the outpatient clinic alongside consultants, which may ultimately be cost saving.

In a recent update to European Association of Urology guidelines for the management of prostate cancer, enzalutamide is listed alongside abiraterone, sipuleucel-T and possibly docetaxel as a potential therapeutic option at PSA progression following initial hormonal therapy in mildly symptomatic or asymptomatic men with no evidence of visceral metastasis.1 Docetaxel, cabazitaxel, abiraterone and enzalutamide are then proposed as options for subsequent lines of treatment. The key trial discussed above was the specific evidence utilised for this guideline.4

In summary therefore the likely use of enzalutamide is consistent with the marketing indication and expert opinion.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of

life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The European Medicines Agency has approved enzalutamide for use in patients with mCRPC in the following situations: a) the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated and b) the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

Enzalutamide and abiraterone are already widely utilised in England in chemo-naïve mCRPC through the Cancer Drugs Fund. These drugs have not been directly compared in randomised controlled clinical trials. Many UK clinicians prefer to use enzalutamide in this setting as it does not require co-administration of corticosteroids. Furthermore, studies of enzalutamide included patients with visceral metastases.4 Enzalutamide is a hepatic enzyme inducer leading to altered pharmacokinetics in several classes of commonly used drugs and therefore will not be suitable for some patients.

Other alternatives include corticosteroids or docetaxel chemotherapy, although many clinicians are reluctant to use chemotherapy in asymptomatic or minimally symptomatic patients given the well described side-effect profile of this cytotoxic therapy. It is important to realise that many men will receive several therapies in sequence. For instance, in a clinical trial of enzalutamide in chemo-naïve mCPRC 33% of patients went on to receive docetaxel. As this trial matures that is expected to increase; 57% received docetaxel following abiraterone in a similar patient group.4,6 Many men initially treated with docetaxel will go on to receive enzalutamide or abiraterone. The optimal sequence of therapies is currently unknown.

Practically, the skills and expertise to deliver this technology are well established in UK cancer centres. Regular biochemical and haematological blood checks, PSAs and imaging (cross-sectional and isotope bone scan) will be required. No IV access or handling of cytotoxic chemotherapy will be required. Acute hospital admissions due to toxicity are expected to be less than with docetaxel chemotherapy. Informal stopping rules are expected to be consistent with clinical trials where enzalutamide was stopped with evidence of radiographic progression, skeletal-related events, clinical progression, initiation of cytotoxic chemotherapy or occurrence of unacceptable toxicity.

The clinical trial included UK cancer centres and it is expected the trial conditions will reflect that observed in clinical practice.

The most important outcomes for this patient group are overall survival, quality of life and treatment related toxicity. All these were measured in the clinical trial.

In general the toxicity profile of this treatment is low and the approach is well tolerated.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Enzalutamide is approved for use in patients previously treated with docetaxel chemotherapy (NICE technology appraisal guidance 316). Furthermore, in England, enzalutamide is available for patients with chemotherapy-naïve castrate-resistant metastatic prostate cancer via the Cancer Drugs Fund. As such, enzalutamide is widely used throughout the UK. Nurse-led and pharmacy-led clinics alongside the consultant-led clinics are easy to develop and should be achievable within three months. It is expected that implementation within a three month time frame would be feasible.

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Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

There are no concerns with regard to equality for this STA.

1. European Association of Urology. Guidelines. http://www.uroweb.org/guidelines/online-guidelines/?no_cache=1
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3. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus Prednisolone or Mitoxantrone plus Prednisolone for Advanced Prostate Cancer. N Engl J Med. 2004;351:1502-12.
4. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371(5):424-33.
5. Rathkopf DE, Smith MR, De bono JS, et al. Updated Interim Efficacy Analysis and Long-term Safety of Abiraterone Acetate in Metastatic Castration-resistant Prostate Cancer Patients Without Prior Chemotherapy (COU-AA-302). Eur Urol. 2014;66(5):815-25.
6. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-60.
7. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411-22.
8. Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-23.
9. De Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364:1995-2005.
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actory prostate cancer. Eur Urol. 2006;50:428-38.