NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA259; Abiraterone for castration-resistant metastatic prostate cancer following previously treated with a docetaxel-containing regimen and TA316; Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen

Original publication date:	TA259: June 2012 TA316: July 2014
Review date	N/A
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA259/316, see Appendix A.

1. Proposal

The guidance should be incorporated into an on-going clinical guideline update. The technology appraisals will remain extant alongside the guideline. That we consult on this proposal.

2. Rationale

There is no new evidence which is likely to lead to a change in the recommendations in either of these guidance documents. Since these appraisals were carried out the treatment pathway for prostate cancer has changed and both abiraterone and enzalutamide can be used earlier in the treatment pathway. There is unlikely to be sufficient evidence for an appraisal of the cost effectiveness of sequential use of these technologies after cytotoxic chemotherapy and the value of such an assessment may have changed since the time technology appraisal 316 was issued because people may now have already had either treatment before having cytotoxic chemotherapy.

The proposal is that the on-going review of Clinical Guideline 175 Prostate Cancer: Diagnosis and Management will include the recommendations of the technology appraisals. The technology appraisals will remain extant alongside the guideline. It will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for a further review.

This option has the effect of preserving the funding direction associated with a positive recommendation in these NICE technology appraisals.

3. Summary of new evidence and implications for review

Has there been any change to the price of the technologies since the guidance was published?
The commercial access agreement for abiraterone has changed since Technology Appraisal (TA) 259 following a re-negotiation by the company with NHS England for TA 387 (Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated) in 2016. It was verified that the renegotiated commercial access agreement does not make abiraterone less cost effective for its indication in TA 259. The patient access scheme for enzalutamide has changed since TA 316 following a re-negotiation by the company with the Department of Health for technology appraisal 377 (Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated). The renegotiated patient access scheme does not make enzalutamide less cost effective for its indication inTA316.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
No.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
Abiraterone was a comparator for enzalutamide in TA316 for the subgroup of people for whom abiraterone is recommended that is, people who have had only 1 prior docetaxel containing chemotherapy regimen. There were no head-to-head trials and an indirect comparison was carried out. Uncertainty surrounding an indirect comparison was noted and no differences in overall survival were found. There have been no head-to-head trials of abiraterone compared with enzalutamide since TA316 was issued. Therefore there is no new evidence to suggest the conclusions on the relative clinical and cost effectiveness of enzalutamide and abiraterone need updating, or considered in a multiple technology appraisal. At the time of TA316 the committee considered the use of enzalutamide after abiraterone and concluded that there was insufficient evidence to determine the clinical or cost effectiveness of the sequential use of abiraterone and enzalutamide after cytotoxic chemotherapy. The Committee made a research recommendation that if enzalutamide is used in routine clinical practice for treating hormone relapsed metastatic prostate cancer that has been treated with abiraterone, data should be collected on resource use and overall survival. The committee further supported the company's ongoing commitment to collect data

on the effectiveness of enzalutamide after previous treatment with abiraterone as part of its pharmacovigilance plan. The manufacturer of enzalutamide has since completed a single arm study (9785-CL-0410), which assessed the PSA response with enzalutamide in people who had previous treatment with abiraterone. This study is now described in the Summary of Product Characteristics (SPC) for enzalutamide. The SPC concluded on this study "Although there was a limited response in some patients from treatment with enzalutamide after abiraterone, the reason for this finding is currently unknown. The study design could neither identify the patients who are likely to benefit, nor the order in which enzalutamide and abiraterone should be optimally sequenced". The searches for this review proposal did not identify any studies assessing the effectiveness of abiraterone taken after enzalutamide. Therefore there remains insufficient data for the committee determine the clinical or cost effectiveness of the sequential use of abiraterone and enzalutamide after chemotherapy. Furthermore, since TA259 and TA316 were issued the treatment pathway for prostate cancer has changed and both abiraterone and enzalutamide have a marketing authorisation and are recommended by NICE as treatment options before chemotherapy is indicated (TA377 and TA387). The decision to use abiraterone, enzalutamide or both sequentially after cytotoxic chemotherapy may now be affected by treatment decisions taken earlier in the treatment pathway.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
The ongoing multi-arm randomised controlled trial STAMPEDE is assessing combinations of treatments for people with prostate cancer starting long-term androgen deprivation therapy (ADT) for the first time, including the use of abiraterone with ADT and enzalutamide with abiraterone. Enzalutamide taken with ADT is additionally being assessed in a separate trial. Therefore, whether there are further points in the treatment pathway where abiraterone and enzalutamide are clinically effective is still being established.

The search strategies from the original assessment reports were re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from February 2015 (the date of the previous review proposal searches)-onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section below. See Appendix C for further details of ongoing and unpublished studies.

4. Equalities issues

The recommendations do not specify a gender to prevent excluding people with prostate cancer who have had gender reassignment treatment.

GE paper sign off: Meindert Boysen, 11 October 2017

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Appendix A – Information from existing guidance

5. Original remit

TA259: *"To appraise the clinical and cost effectiveness of abiraterone in combination with prednisolone within its licensed indication for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy".*

TA316: *"To appraise the clinical and cost effectiveness of enzalutamide within its licensed indication for the treatment of metastatic hormone relapsed prostate cancer previously treated with a docetaxel-containing regimen".*

6. Current guidance

TA259

1.1 Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, only if:

- their disease has progressed on or after one docetaxel-containing chemotherapy regimen, and
- the manufacturer provides abiraterone in accordance with the commercial access arrangement as agreed with NHS England.

1.2 People currently receiving abiraterone in combination with prednisone or prednisolone whose disease does not meet the criteria in 1.1 should be able to continue therapy until they and their clinician consider it appropriate to stop.

TA316

1.1 Enzalutamide is recommended within its marketing authorisation as an option for treating metastatic hormone-relapsed prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy, only if the manufacturer provides enzalutamide with the discount agreed in the patient access scheme.

1.2 The use of enzalutamide for treating metastatic hormone-relapsed prostate cancer previously treated with abiraterone is not covered by this guidance.

7. Research recommendations from original guidance

TA259

No research recommendations were made.

TA316

- *"The Committee supports the manufacturer's ongoing commitment to collect data on the effectiveness of enzalutamide after previous treatment with abiraterone.*

- *The Committee considered that if enzalutamide is used in routine clinical practice for treating hormone relapsed metastatic prostate cancer that has been previously treated with abiraterone, data should be collected on resource use and overall survival".*

Cost information from original guidance

Conditional on (confidential) access arreangements.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A review of the guidance should be planned into the appraisal work programme. The review will be conducted through the specify STA or MTA process.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred to specify date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	**Yes**

Appendix B

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.

Appendix C – other relevant information

1. Relevant Institute work

Published

Prostate cancer (2015) NICE quality standard QS91

Prostate cancer: diagnosis and management (2014) NICE guideline CG175

Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (2016) NICE technology appraisal guidance TA391

Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (2016) NICE technology appraisal guidance 412

Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours (2012) NICE technology appraisal guidance 265

Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (2016) NICE technology appraisal guidance 377

Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (2016) NICE technology appraisal guidance 387

In progress

Prostate cancer: diagnosis and management (update). NICE guideline. Publication expected: January 2019.

2. Details of new products

Drug (company)	Details (phase of development, expected launch date)	In topic selection
Enzalutamide (new tablet formulation) (Astellas)	Pre-registration filings made in Europe for metastatic castration-resistant prostate cancer in men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, and in men whose disease has progressed on or after docetaxel therapy.	Not applicable
Custiren (OncoGenex)	Phase III for the treatment of hormone-refractory disease as second-line chemotherapy.	No
Relugolix (Myovant Sciences)	Phase III for treatment of advanced prostate cancer (treatment line not specified by NHS Specialist Pharmacy Service)	No
Rilimogene galvacirepvec-rilimogene glafolivec (Bristol-Myers Squibb)	Phase III for treatment of advanced prostate cancer (treatment line not specified by NHS Specialist Pharmacy Service)	Yes

3. Details of changes to the indications of the technology

Indication and considered in original appraisal	Proposed indication (for this appraisal) and current price
Abiraterone: *"…with prednisone or prednisolone for the treatment of metastatic*	No change to licensed indications (relevant to this review proposal) for either drug.

Indication and considered in original appraisal	Proposed indication (for this appraisal) and current price
castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen". Enzalutamide: *"…treatment of adult men with metastatic castrate-resistant prostate cancer whose disease has progressed on or after docetaxel therapy".*	Access to both drugs is currently contingent on Patient Access Schemes.

4. Registered and unpublished trials

Trial name and registration number	Details
Study of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men With Metastatic Castration-Resistant Prostate Cancer (PROfound Study) NCT02987543; D081DC00007.	n = 340 Estimated primary completion date: January 2020 Estimated overall completion date: February 2021
Cabazitaxel Versus the Switch to Alternative AR-targeted Agent (Enzalutamide or Abiraterone) in Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients Previously Treated With Docetaxel and Who Rapidly Failed a Prior AR-targeted Agent NCT02485691; LPS14201; 2014-004676-29; U1111-1166-5329; CARD	n = 324 Estimated completion date: June 2018
A Study That Provides Long-term Safety Follow-up and Examines Long-term Exposure to Abiraterone Acetate NCT01517802; CR100797; 212082PCR3010; 2011-005243-28	Long-term, single-arm follow-up of participants from previous abiraterone trials. n = 300 Estimated completion date: April 2018

Appendix D

Trial name and registration number	Details
Enzalutamide With or Without Abiraterone and Prednisone in Treating Patients With Castration-Resistant Metastatic Prostate Cancer NCT01949337; A031201; U10CA031946; NCI-2013-01737	n = 1311 Estimated completion date: December 2019
Cognitive Effects of Androgen Receptor Directed Therapies for Advanced Prostate Cancer NCT03016741; VICC URO 16133; NCI-2016-01795	Abiraterone + prednisone vs. enzalutamide n = 100 Estimated primary completion date: August 2018 Estimated overall completion date: August 2019
Discovery Stage Clinical Study About Oncology Drugs and Single Nucleotide Polymorphisms NCT02403505; Drugs-SNPs; ANDA208414; FWA00015357; IORG0007849; IRB00009424; ANDA208414; IND78420; NPI1831468511; NPI1023387701	Abiraterone + prednisone + either enzalutamide or nilandron n = 600 Estimated completion date: August 2020
A Study of Abiraterone Acetate Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy NCT01695135; CR100010; ABI-PRO-3001	Randomised controlled trial vs. placebo in Asian participants. n = 214 Primary completion date: June 2014 Estimated overall completion date: December 2017