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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2020

Niraparib for metastatic castration-resistant prostate cancer with DNA-repair anomalies

NIHRIO ID	13159	**NICE ID**	10101
Developer/Company	GlaxoSmithKline UK Ltd	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Niraparib is in clinical development for the treatment of metastatic castrate-resistant prostate cancer (mCRPC) with DNA-repair anomalies. Prostate cancer is the most common type of cancer in men in the UK. The cancer is called advanced (metastatic) prostate cancer when the cancer cells have spread to other parts of the body like bones, lymph nodes outside the pelvis or rarely to the liver or lungs. It is not possible to cure metastatic prostate cancer but is possible to keep it under control. Prostate cancers that continue to grow despite hormonal therapies are called "castration-resistant" prostate cancer. In some mCRPC, mutations in several genes involved in DNA damage repair have been reported and treatments that target these DNA anomalies are being developed.

Niraparib is a medicinal product taken orally. It works by blocking a protein called poly (adenosine diphosphate-ribose) polymerase (PARP). It blocks the action of PARP-1 and PARP-2 enzymes that help in repairing damaged DNA in cells when they divide to make new cells. By blocking PARP enzymes, the damaged DNA in cancer cells cannot be repaired, and the cells die. If licensed, niraparib will offer an additional treatment option for men with mCRPC with DNA-repair anomalies.

PROPOSED INDICATION

For the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) with DNA-repair anomalies (and BRCA1/2 gene-mutation), who have received prior taxane chemotherapy and androgen-receptor (AR)-targeted therapy.[1]

TECHNOLOGY

DESCRIPTION

Niraparib (Zejula, JNJ-64091742, MK-4827) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which plays a role in DNA repair. In vitro studies have shown that niraparib may involve inhibition of PARP enzymatic activity and increased the formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death.[2]

Niraparib is currently in phase II clinical development for men with mCRPC and characterised as having DNA repair anomalies. In phase II clinical trial (Galahad; NCT02854436), participants will receive 300 milligram (mg) niraparib (3 capsules*100 mg) orally once daily.[1]

INNOVATION AND/OR ADVANTAGES

Hormone therapy (androgen deprivation or anti-androgens) is currently the primary treatment for metastatic prostate cancer.[3] Currently, there is a clinical need and urgency for additional treatments that are well tolerated and that can improve outcomes in prostate cancer patients, especially in those with metastatic castration-resistant disease. PARP proteins play a key role in DNA repair mechanisms and represent a valid target for new therapies.[4]

The benefits of hormone treatments for men with prostate cancer that has metastasised do not last. Over time, many prostate cancers continue to grow despite hormonal therapies (and are called "castration-resistant" prostate cancer). Niraparib works by inhibiting PARP, a protein that helps cancer cells repair DNA that has been damaged by cancer treatments. When cancer cells repair damaged DNA, they can continue growing and multiplying, so depriving them of this power with a PARP inhibitor may be an effective approach to treatment.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, niraparib is licensed in the EU/UK as a monotherapy for maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.[2]

The most common adverse events (≥ 10%) among patients receiving niraparib monotherapy were nausea, thrombocytopenia, fatigue/asthenia, anaemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decrease appetite, nasopharyngitis, diarrhoea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia.[2]

Niraparib is currently in phase III and phase II clinical development for the treatment of various types of cancers including: ovarian cancer, fallopian tube cancer, pancreatic cancer, metastatic melanoma, endometrial cancer, and others.[6]

Niraparib has a Breakthrough Therapy designation by the US FDA for mCRPC in October 2019.[7]

PATIENT GROUP

DISEASE BACKGROUND

Prostate cancer is cancer of the prostate gland.[8] Usually, prostate cancer grows slowly so there may be no signs for many years.[9] Some prostate cancers grow faster and need to be treated to stop them spreading. Metastatic prostate cancer occurs when the cancer cells have spread to other parts of the body. The most common place for prostate cancer to spread to is the bones. It may also spread to lymph nodes outside the pelvis or rarely to the liver or the lungs. It is not possible to cure metastatic prostate cancer. Metastatic prostate cancer may develop in men who have previously been treated for prostate cancer. In some men, prostate cancer is first diagnosed when cancer has already reached an advanced stage.[9,10]

Prostate cancer growth and proliferation are primarily dependent on androgens, and androgen deprivation therapy (ADT) is an effective means of controlling the disease. However, some men develop resistance to androgen deprivation, resulting in the development of castration-resistant prostate cancer (CRPC).[11]

Inherited mutations in several genes involved in DNA damage repair have been reported to predispose men to prostate cancer.[12-15] Normal cells are less subjected to DNA damage than tumour cells and, therefore, less influenced by inhibitors of DNA repair mechanisms. DNA damage can be acquired in cells over time through exposure to exogenous chemicals and physical agents or endogenous reactive metabolites including reactive oxygen and nitrogen species. The nuclear PARP enzymes are physiologically involved in multiple aspects of DNA repair and transcription regulation. Efficient and correct repair of DNA damage is critical for cellular survival.[4]

Although the cause of prostate cancer is unknown, a man's risk of developing prostate cancer depends on many factors such as age, ethnicity, being overweight or obese, genetics and family history, lifestyle factors, and other medical conditions.[10] Patients might have specific symptoms depending on where cancer has spread. Prostate cancer does not usually cause any symptoms until cancer has grown large enough to put pressure on the urethra. Symptoms of prostate cancer can include: needing to urinate more frequently, often during the night, needing to rush to the toilet, difficulty in starting to urinate, straining or taking a long time while urinating, weak flow, feeling that the bladder has not emptied fully, blood in urine or in semen, fatigue, feeling generally unwell, and have weight loss for no known reason.[16,17]

Prostate cancer is a significant cause of morbidity and mortality in men, especially in those over the age of 75 years and impacts on their daily lives, particularly physical and emotional health, relationships and social life.[18]

CLINICAL NEED AND BURDEN OF DISEASE

There were approximately 47,700 new cases of prostate cancer in the UK in 2014-2016.[19] The age-standardised incidence rate in England for prostate cancer, in 2016, was 80.4 per 100,000 males.[20] Genetic sequencing studies have shown that deleterious germline mutations in damaged DNA repair genes are present in 8% to 12% of patients with mCRPC.[21-23]

More prostate cancer patients are diagnosed at an early stage (57-63% diagnosed at stage I or II) than a late stage (37-43% diagnosed at stage III or IV) in England and Northern Ireland.[24] In 2016, prostate cancer was the most common cancer in males in the UK, accounting for 26%

of all new cancer cases in males. Across all genders, prostate cancer is the 2nd most common cancer in the UK, accounting for 13% of all new cancer cases (2016).[20] According to statistical analysis, the incidence rates for prostate cancer are projected to rise by 12% in the UK between 2014 and 2035, from 208 cases per 100,000 males in 2014 to 233 cases per 100,000 males by 2035.[25]

Prostate cancer incidence is strongly related to age, with the highest incidence rates being in older men. In the UK in 2014-2016, on average each year more than a third (35%) of new cases were in males aged 75 years and over.[26] In England, in 2018-2019, there were 86,487 finished consultant episodes (FCE) for malignant neoplasm of prostate (ICD 10: C61), resulting in 81,227 hospital admissions and 92,702 FCE bed days.[27]

There are around 11,700 prostate cancer deaths every year, accounting for 14% of all cancer deaths in males in the UK in 2017. Mortality rates for prostate cancer are projected to fall by 16% in the UK between 2014 and 2035, to 48 deaths per 100,000 males by 2035.[28]

Men diagnosed with prostate cancer in England and Wales have shown high survival rates. More than 8 in 10 (84%) men diagnosed with prostate cancer survive their disease for ten years or more. Around 85% of men diagnosed with prostate cancer survive for five years or more and 94% of men survive their disease for one year or more (2010-2011 data). Prostate cancer survival in England is highest for men diagnosed aged 60-69 years old, probably because of PSA testing detecting latent, earlier, slow-growing cancers (2009-2013 data).[29]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The decision about the best approach to treat and care for cancer should be discussed among a multidisciplinary team and the choice of treatment depends on several factors such as where the cancer is, how far it has grown or spread (the stage), type of cancer, how abnormal the cells look under a microscope (the grade), and general health and level of fitness of the patient. In general, there is no treatment straight away but the main treatments are surgery, external radiotherapy, brachytherapy, hormone therapy (androgen deprivation or anti-androgens), chemotherapy, and symptom control treatment.[30]

CURRENT TREATMENT OPTIONS

For men with mCRPC who have received prior taxane chemotherapy (Docetaxel), NICE recommends:[31]

- Abiraterone in combination with prednisone or prednisolone is recommended as an option for the treatment of castration-resistant metastatic prostate cancer in adults, in which the disease has progressed on or after one docetaxel-containing chemotherapy regimen;
- Enzalutamide is recommended as an option for treating metastatic hormone-relapsed prostate cancer in adults whose disease has progressed during or after docetaxel-containing chemotherapy;
- Cabazitaxel in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people whose disease has progressed during or after docetaxel chemotherapy, only if: the person has an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; the person has had 225 mg/m^2 or more of docetaxel; treatment with cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first).

PLACE OF TECHNOLOGY

If licensed, niraparib will offer an additional treatment option for patients with BRCA1/2 gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have received prior taxane chemotherapy and AR-targeted therapy.

CLINICAL TRIAL INFORMATION

Trial	**Galahad**, NCT02854436, EudraCT 2016-002057-38; A Phase 2 Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies **Phase II** **Location(s):** EU (including the UK), USA, Canada, and other countries
Trial design	Multicentre, open-label and single group assignment
Population	n=301 (planned); aged 18 and older with a histological confirmed prostate cancer (mixed histology is acceptable, with the exception of the small cell pure phenotype, which is excluded); received a taxane-based chemotherapy for the treatment of metastatic prostate cancer with evidence of disease progression on or after treatment, or discontinued from a taxane-based chemotherapy due to an adverse event; received a second-generation or later androgen receptor (AR)-targeted therapy (for example, abiraterone acetate plus prednisone, enzalutamide, apalutamide) for the treatment of metastatic prostate cancer with evidence of disease progression or non-metastatic castration-resistant prostate cancer with evidence of subsequent metastasis; biomarker-positive by at least one of the following criteria: (a) Biallelic deoxyribonucleic acid (DNA)-repair anomaly based on a sponsor validated blood or tissue assay; (b) Germline pathogenic Breast Cancer gene (BRCA) 1 or BRCA2 by any test; and progression of metastatic prostate cancer in the setting of castrate levels of testosterone or history of bilateral orchiectomy at study entry.
Intervention(s)	Participants will receive niraparib, 300 mg (3 capsules*100 mg) orally once daily.
Comparator(s)	-
Outcome(s)	Objective Response Rate (ORR) [Time frame: screening, cycle 1 (each cycle of 28 days) day 1 (every 8 weeks for the first 6 months and then every 12 weeks thereafter) till follow-up phase] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Niraparib is already marketed in the UK. The NHS indicative price is:[32]

- a pack of 56 x 100 mg capsules costs £4,500.00
- a pack of 84 x 100 mg capsules costs £6,750.00.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Radium–223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). September 2016.
- NICE Technology Appraisal guidance. Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (TA391). May 2016 (Last updated: August 2016).
- NICE Technology Appraisal guidance. Abiraterone for treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy (TA259). June 2012 (Last updated: July 2016).
- NICE Technology Appraisal guidance. Abiraterone for treating metastatic hormone-relapsed prostate cancer before chemotherapy (TA387). April 2016.
- NICE technology appraisal guidance. Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated (TA377). January 2016.
- NICE technology appraisal guidance. Enzalutamide for metastatic hormone-relapsed prostate cancer previously treated with a docetaxel-containing regimen (TA316). July 2014.
- NICE Clinical Guideline. Prostate cancer: diagnosis and management (NG131). May 2019.
- NICE quality standard. Prostate cancer (QS91). June 2015. (Last updated: May 2019).

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a.
- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) in the treatment of Prostate Cancer. 16031/P. July 2016.
- NHS England. Clinical Commissioning Policy: Proton Beam Therapy for Cancer of the Prostate. 16020/P. July 2016.

OTHER GUIDANCE

- European Society for Medical Oncology. Cancer of the Prostate: ESMO Clinical Practice Guidelines. 2015. (Updates: 2016, 2017).[33]
- European Association of Urology (EAU) – European Society for Radiotherapy & Oncology (ESTRO) – European Society of Urogenital Radiology (ESUR) – International Society of Geriatric Oncology (SIOG) Guidelines on Prostate Cancer. 2017.[34]

ADDITIONAL INFORMATION

GlaxoSmithKline UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

1 ClinicalTrials.gov. *An Efficacy and Safety Study of Niraparib in Men With Metastatic Castration-Resistant Prostate Cancer and DNA-Repair Anomalies (Galahad)*. *Trial ID*. Status: Available from: https://clinicaltrials.gov/ct2/show/NCT02854436 [Accessed 09 January 2020].

2 electronic Medicines Compendium (eMC). *Zezula 100 mg hard capsules.* Available from: https://www.medicines.org.uk/emc/product/8828 [Accessed 09 January 2020].

3 British National Formulary (BNF). *Prostate Cancer.* Available from: https://bnf.nice.org.uk/treatment-summary/prostate-cancer.html [Accessed 09 January 2020].

4 De Felice, F., Tombolini V., Marampon F., Musella A., Marchetti C. *Defective DNA repair mechanisms in prostate cancer: impact of olaparib*. Drug Des Devel Ther. 2017;11:547-52. Available from: 10.2147/DDDT.S110264 https://www.ncbi.nlm.nih.gov/pubmed/28280302

5 Memorial Sloan Kettering Cancer Center. *A Phase II Study of Niraparib for Men with Metastatic Castration-Resistant Prostate Cancer and DNA Repair Problems.* Available from: https://www.mskcc.org/cancer-care/clinical-trials/18-068 [Accessed 17 January 2019].

6 ClinicalTrials.gov. *Niraparib - Phase II and III clinical trial*. *Trial ID*. Status: Available from: https://clinicaltrials.gov/ct2/results?cond=niraparib+&term=&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 09 January 2020].

7 Cision PR Newswire. *Janssen Announces U.S. FDA Breakthrough Therapy Designation Granted for Niraparib for the Treatment of Metastatic Castration-Resistant Prostate Cancer.* Available from: https://www.prnewswire.com/news-releases/janssen-announces-us-fda-breakthrough-therapy-designation-granted-for-niraparib-for-the-treatment-of-metastatic-castration-resistant-prostate-cancer-300930955.html [Accessed 17 January 2020].

8 Cancer Research UK. *What is prostate cancer?* Available from: https://about-cancer.cancerresearchuk.org/about-cancer/prostate-cancer/about [Accessed 17 January 2020].

9 National health Service. *Overview - Prostate cancer.* Available from: https://www.nhs.uk/conditions/prostate-cancer/ [Accessed 09 January 2020].

10 Cancer Research UK. *About prostate cancer.* Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/about [Accessed 09 January 2020].

11 Anantharaman, A., Friedlander T. W. *Targeting the androgen receptor in metastatic castrate-resistant prostate cancer: A review*. Urol Oncol. 2016 Aug;34(8):356-67. Available from: 10.1016/j.urolonc.2015.11.003 https://www.ncbi.nlm.nih.gov/pubmed/26706121

12 Dombernowsky, S. L., Weischer M., Allin K. H., Bojesen S. E., Tybjaerg-Hansen A., Nordestgaard B. G. *Risk of cancer by ATM missense mutations in the general population*. J Clin Oncol. 2008 Jun 20;26(18):3057-62. Available from: 10.1200/JCO.2007.14.6613 https://www.ncbi.nlm.nih.gov/pubmed/18565893

13 Eeles, R., Goh C., Castro E., Bancroft E., Guy M., Al Olama A. A., et al. *The genetic epidemiology of prostate cancer and its clinical implications*. Nat Rev Urol. 2014 Jan;11(1):18-31. Available from: 10.1038/nrurol.2013.266 https://www.ncbi.nlm.nih.gov/pubmed/24296704

14 Erkko, H., Xia B., Nikkila J., Schleutker J., Syrjakoski K., Mannermaa A., et al. *A recurrent mutation in PALB2 in Finnish cancer families*. Nature. 2007 Mar 15;446(7133):316-9. Available from: 10.1038/nature05609 https://www.ncbi.nlm.nih.gov/pubmed/17287723

15 Leongamornlert, D., Mahmud N., Tymrakiewicz M., Saunders E., Dadaev T., Castro E., et al. *Germline BRCA1 mutations increase prostate cancer risk*. Br J Cancer. 2012 May 8;106(10):1697-701. Available from: 10.1038/bjc.2012.146 https://www.ncbi.nlm.nih.gov/pubmed/22516946

16 Cancer Research UK. *Symptoms of advanced cancer.* Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/advanced-cancer/symptoms-advanced-cancer [Accessed 09 January 2020].
17 National Health Service. *Symptoms - Prostate cancer.* Available from: https://www.nhs.uk/conditions/prostate-cancer/symptoms/ [Accessed 09 January 2020].
18 Appleton L, W. D., Perkins E, Parker C, Crane J, et al. *The impact of prostate cancer on men's everyday life*. European Journal of Cancer Care. 2015;24:71-84. Available from: 10.1111/ecc.12233 https://doi.org/10.1111/ecc.12233
19 Cancer Research UK. *Prostate cancer statistics - Prostate cancer incidence.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero [Accessed 10 January 2020].
20 Cancer Research UK. *Prostate cancer incidence statistics - Prostate cancer incidence by UK country.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence#heading-Zero [Accessed 10 January 2020].
21 Annala, M., Struss W. J., Warner E. W., Beja K., Vandekerkhove G., Wong A., et al. *Treatment Outcomes and Tumor Loss of Heterozygosity in Germline DNA Repair-deficient Prostate Cancer*. Eur Urol. 2017 Jul;72(1):34-42. Available from: 10.1016/j.eururo.2017.02.023 https://www.ncbi.nlm.nih.gov/pubmed/28259476
22 Pritchard, C. C., Mateo J., Walsh M. F., De Sarkar N., Abida W., Beltran H., et al. *Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer*. N Engl J Med. 2016 Aug 4;375(5):443-53. Available from: 10.1056/NEJMoa1603144 https://www.ncbi.nlm.nih.gov/pubmed/27433846
23 Robinson, D., Van Allen E. M., Wu Y. M., Schultz N., Lonigro R. J., Mosquera J. M., et al. *Integrative Clinical Genomics of Advanced Prostate Cancer*. Cell. 2015 Jul 16;162(2):454. Available from: 10.1016/j.cell.2015.06.053 https://www.ncbi.nlm.nih.gov/pubmed/28843286
24 Cancer Research UK. *Prostate cancer incidence statistics - Prostate cancer incidence by stage at diagnosis.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence#heading-Three [Accessed 10 January 2020].
25 Cancer Research UK. *Cancer incidence for common cancers - Projections of incidence for common cancers.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Four [Accessed 10 January 2019].
26 Cancer Research UK. *Prostate cancer incidence statistics - Prostate cancer incidence by age.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence#heading-One [Accessed 10 January 2020].
27 NHS Digital. *Hospital Admitted Patient Care Activity, 2018-19.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2018-19 [Accessed 10 January 2020].
28 Cancer Research UK. *Prostate cancer statistics - Prostate cancer mortatily.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-One [Accessed 10 January 2020].
29 Cancer Research UK. *Prostate cancer statistics - Prostate cancer survival.* Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Two [Accessed 10 January 2020].
30 Cancer Research UK. *Decisions about your treatment.* Available from: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/treatment/decisions-about-your-treatment [Accessed 10 January 2020].
31 National Institute for Health and Care Excellence (NICE). *Treating hormone-relapsed metastatic prostate cancer.* Available from: https://pathways.nice.org.uk/pathways/prostate-cancer#path=view%3A/pathways/prostate-cancer/treating-hormone-relapsed-metastatic-

prostate-cancer.xml&content=view-node%3Anodes-treatment-options-after-chemotherapy-with-a-docetaxel-regimen [Accessed 21 February 2020].

32 British National Formulary (BNF). *Niraparib.* Available from: https://bnf.nice.org.uk/medicinal-forms/niraparib.html [Accessed 10 January 2020].

33 Parker, C., Gillessen S., Heidenreich A., Horwich A. *Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up*. Ann Oncol. 2015 Sep;26 Suppl 5:v69-77. Available from: 10.1093/annonc/mdv222 https://www.ncbi.nlm.nih.gov/pubmed/26205393

34 European Association of Urology. *EAU - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer.* Available from: https://uroweb.org/wp-content/uploads/09-Prostate-Cancer_2017_web.pdf [Accessed 14 January 2019].

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