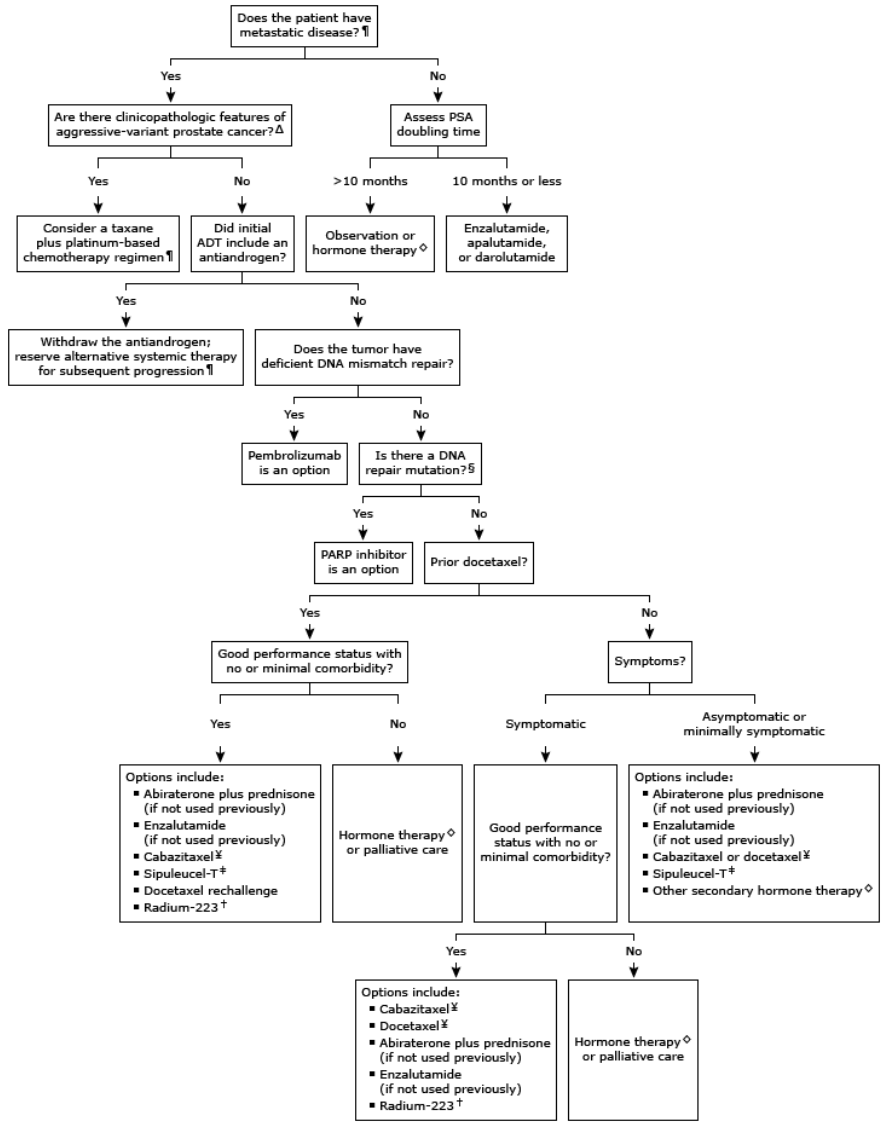
A.11	Enzalutamide – metastatic castration-resistant prostate cancer
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: According to the Global Cancer Patterns 2020, prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men, with an estimated almost 1.4 million new cases and 375,000 deaths worldwide. Incidence rates vary from 6.3 to 83.4 per 100,000 men across regions, with the highest rates found in Northern and Western Europe, the Caribbean, Australia/New Zealand, Northern America, and Southern Africa and the lowest rates in Asia and Northern Africa. Regional patterns of mortality rates do not follow those of incidence, with the highest mortality rates in the Caribbean, sub-Saharan Africa, and Micronesia/Polynesia. This is mainly due to the fact that screening for prostate cancer is not common in these regions and a large proportion of prostate cancer patients present at a late stage. The mortality rate for prostate cancer in Africa and the Caribbean is more than twice the world average (Sung 2021) Men with advanced prostate cancer who have evidence of disease progression (e.g., an increase in serum prostate-specific antigen (PSA), new metastases, or progression of existing metastases) while being managed with androgen deprivation therapy (ADT) and who have castrate levels of serum testosterone (<50 ng/dL) are considered to have metastatic castration-resistant prostate cancer (CRPC). There are no widely accepted criteria to define the emergence of CRPC when the only evidence of disease progression is an increase in serum PSA. This decision requires judgment from the treating clinician; thus practice is variable. CRPC includes a heterogeneous population, from subjects with a prostate-specific antigen (PSA)-only recurrence (M0 disease with a rising PSA and no demonstrable metastases) to men with extensive, high-volume, symptomatic, metastatic disease in visceral sites and/or bone. The most important factor influencing survival in men with CRPC is the site and extent of metastatic involvement (Dawson 2021).
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	The Application regards the inclusion of enzalutamide for metastatic castration-resistant prostate cancer (CRPC) in the Model List. The Application clearly report that the non-metastatic prostate cancer setting is not included as data on the use of enzalutamide are not enough mature. Androgen deprivation therapy (ADT) with or without chemotherapy is generally the initial treatment for metastatic prostate cancer. Initial response rate is usually high (80-90%) but several men eventually develop progressive disease after ADT (CRPC). At the CRPC stage, the disease is no longer responsive to ADT and other medications should be used to interfere with the androgenic stimulation. Multiple agents have been shown to improve overall survival (OS) in metastatic CRPC, all given in conjunction with continued ADT: 1. Inhibition of androgen biosynthesis (abiraterone) Abiraterone in combination with prednisone is one of the preferred systemic approach after progression on ADT. Abiraterone, a derivative of steroidal progesterone, is already included in the Model List for refractory prostate cancer. According to a recent Cochrane review, the addition of abiraterone to ADT reduces the probability of death from any cause compared to ADT alone (hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.56 to 0.73; 2 RCTs, 2201 men; high certainty of evidence). It also results in little to no difference in quality of life compared to ADT alone, measured with the Functional Assessment of Cancer Therapy-prostate total

	score (Sathianathen 2020). 2. Interference with androgenic stimulation of prostate cancer growth (enzalutamide, apalutamide, darolutamide). These agents are alternative options that can be preferred based on their different safety profile and as they can be used without prednisone. 3. Chemotherapy using a taxane (docetaxel, cabazitaxel). Taxanes are the only agents for which a survival benefit has been demonstrated in metastatic CRPC. Cytotoxic chemotherapy with a taxane is generally reserved for patients with relatively rapidly progressing symptomatic disease for which less toxic approaches (e.g., abiraterone, enzalutamide) are not appropriate options. 4. Immunotherapy. Sipuleucel-T is an option for minimally symptomatic men who have slowly progressive disease not requiring a rapid response. In addition, men whose tumors have dMMR (or are microsatellite unstable) or who have overexpression of programmed cell death ligand 1 (PD-L1) are candidates for immunotherapy using an immune checkpoint inhibitor. 5. For men with a DNA mismatch repair mutation (eg, in a BRCA gene or another gene such as PALB2) as determined by germline testing, next-generation sequencing of tumor tissue, or assay of circulating free DNA, treatment with a PARP inhibitor is an option.



Source: Dawson 2021

Direct comparisons, as for instance between abiraterone plus prednisone and enzalutamide, are lacking. The choice of initial therapy is largely driven by considerations on the size and extension of the disease and previous lines of treatment, as systemic therapies are currently increasingly used also in the hormone-sensitive phase along with ADT. Other factors include route and frequency of administration, safety profile, costs, and patients' preferences. It should be noted that enzalutamide can be used without corticosteroids.

The optimal sequence and the added value of combinations of treatments are largely unknown. Moreover, evidence suggests cross-resistance between abiraterone and enzalutamide.

ESMO guidelines report the following recommendations for metastatic CRPC (Parker 2020)

-Abiraterone or enzalutamide [ESMO-MCBS v1.1 scores: 4] is recommended for first line asymptomatic/mildly symptomatic men [I, A].

-Docetaxel [ESMO-MCBS v1.1 score: 4] is recommended for men with mCRPC [I, A].

In the second line post-docetaxel, abiraterone [ESMO-MCBS v1.1 score: 4], enzalutamide [ESMO-MCBS v1.1 score: 4] or cabazitaxel [ESMOMCBS v1.1 score: 3]

	are recommended options [I, A]. -The use of a second androgen receptor inhibitor (abiraterone after enzalutamide or vice versa) is not recommended [II, D].
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☒ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: The Application reports data from the following phase III trials in non-metastatic and metastatic CRPC. It also includes studies concerning hormone-sensitive prostate cancer that are not directly pertinent to the scope of the Application. The Application does not include data on drugs with a similar mechanism of action, apalutamide, darolutamide. <u>Metastatic</u> -pivotal study AFFIRM (2nd line): 1,199 adults with metastatic CRPC who had previously taken docetaxel were randomized to enzalutamide or placebo. At the cut-off date for the interim analysis, the median follow-up time was 14.4 months. OS was found to be 18.4 months for enzalutamide and 13.6 months for the control arm [Hazard ratio (HR) 0.63; 95% CI 0.53 to 0.75]. PFS was 8.3 for enzalutamide versus 2.9 for the placebo [HR 0.40; 95% 0.35 to 0.47]. Data on quality of life (QoL), collected in a subgroup using EQ-5D and Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaires, suggested a possible benefit. The study was halted after interim results were collected due to the benefits shown by enzalutamide. -PREVAIL (1st line): 1,717 patients with mCRPC who had not yet received chemotherapy. This placebo-controlled trial was halted after interim results were collected due to the benefits shown by enzalutamide. The co-primary end points were radiographic progression-free survival and overall survival. Enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of chemotherapy. A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data cut-off date (29% reduction in the risk of death; HR, 0.71; 95% CI, 0.60 to 0.84). <u>Non metastatic</u> *(not directly pertaining to this Application)* Although the Application regards the metastatic setting data from the PROSPER trial were also included. PROSPER enrolled 1401 men with **non-metastatic CRPC** receiving androgen-deprivation therapy were randomly assigned (in a 2:1 ratio) to receive enzalutamide at a dose of 160 mg or placebo once daily. Median OS was 67.0 months (95% CI, 64.0 to not reached) in the enzalutamide group and 56.3 months (95% CI, 54.4 to 63.0) in the placebo group (hazard ratio for death, 0.73; 95% CI, 0.61 to 0.89). It should be noted that patients enrolled in this trial had to stop bicalutamide therapy before randomization. One concurrent study (STRIVE trial) compared enzalutamide and standard bicalutamide for the same indication (Hilal e Prasad 2019) and showed that PFS was significantly longer with enzalutamide only afterward. *Metastatic hormone-sensitive prostate cancer (not directly pertaining to this Application)* -ENZAMET (1st / 2nd line): 1125 men randomly assigned to receive open-label enzalutamide (160 mg daily) or a standard nonsteroidal antiandrogen drug (standard-

	care group) enzalutamide was associated with significantly longer progression-free and overall survival (HR, 0.67; 95% CI, 0.52 to 0.86) than standard care in men with **metastatic, hormone-sensitive prostate cancer** receiving testosterone suppression. -ARCHES (1st / 2nd line): 1150 men with **metastatic hormone-sensitive prostate cancer** were randomly assigned to enzalutamide (160 mg/day) or placebo, plus ADT, stratified by disease volume and prior docetaxel chemotherapy. The primary end point was radiographic progression-free survival. The risk of radiographic progression or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (hazard ratio, 0.39; 95% CI, 0.30 to 0.50; median not reached v 19.0 months). *Sequence treatment* A multicentre, randomised, open-label, phase 2, crossover trial suggested that using a sequencing strategy of abiraterone acetate followed by enzalutamide provides the greatest clinical benefit (Khalaf 2019). Better survival outcomes were reported in several observational studies where patients with advanced prostate cancer received the abiraterone to enzalutamide sequence compared with the enzalutamide to abiraterone sequence (Mori 2020, Pereira-Salgado 2020) The CARD trial compared cabazitaxel and a second androgen receptor inhibitor (abiraterone or enzalutamide, depending on the use of a previous androgen-signaling–targeted inhibitor. The median OS was 13.6 months with cabazitaxel and 11.0 months with the second androgen-signalling targeted inhibitor (HR 0.64; 95% CI, 0.46 - 0.89). In the control arm, the response rate and the duration of response to a second androgen receptor inhibitor were poor, confirming the results from previous studies. This is probably due to the fact that these agents target the same pathway and thus share common mechanisms of resistance. The CARD trial has not been included in the Application.
Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable **Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s).** In metastatic CRPC evidence of benefit of the use of enzalutamide comes from trials in post-docetaxel or naïve patients. In the second line after chemotherapy, enzalutamide appears to increase OS and PFS of about 5 months and significantly improve quality of life (AFFIRM study) over placebo. In the first line (men with minimally symptomatic or asymptomatic metastatic CPRC who had not received cytotoxic chemotherapy, ketoconazole, or abiraterone acetate) enzalutamide provides a substantial benefit in terms of radiographic PFS and delayed the initiation of chemotherapy over placebo. The median overall survival was estimated at 32.4 months in the enzalutamide group and 30.2 months in the placebo group (PREVAIL trial). *Information not directly pertinent to the scope of Application* In non-metastatic CRPC evidence of benefit of the use of enzalutamide derives from the PROSPER trial. A significant benefit was observed in terms of metastasis-free survival, median time to PSA progression and time to subsequent antineoplastic therapy. Data on OS are immature but suggest a possible longer survival of about 1 year over placebo. In metastatic hormone-naïve prostate cancer the addition of enzalutamide to ADT

	may provide some benefits in terms of PFS and OS but other alternatives exist with more robust evidence supporting their use. Since no biomarkers have been identified to select one therapy over another, the decision to use abiraterone, apalutamide, enzalutamide or docetaxel should be individualised taking into consideration cost, access to treatment, toxicity profiles, duration of treatment, comorbidities and patient preferences (ESMO guidelines) **Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)?** Not specific.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: In clinical trials the most common adverse events were fatigue/asthenia, back pain, hot flush, falls, hypertension and other adverse cardiovascular events. Neurological disorders have been described which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension (Posterior reversible encephalopathy syndrome, PRES). Since survival in metastatic CRPC has improved substantially, long-term toxicity of treatments should be carefully considered. Data on long-term risks to bone and sexual health are poor. Enzalutamide can cause fetal harm and loss of pregnancy. Males with female partners of reproductive potential should use effective contraception.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Overall, considering the totality of the evidence it appears that the benefit-harm profile of enzalutamide in patients with CRPC is favourable but the magnitude of the effect in terms of OS and QoL is not fully defined, especially compared to other available alternative treatments. The lack of comparative evidence makes it difficult to select the first line treatment of choice in patients with metastatic CRPC.

Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The overall quality of judged to be moderate. Considering the metastatic setting only, two trials (AFFIRM, PREVAIL) can be considered at low risk of bias (adequate randomisation and double-blind design) but they were both stopped at interim, thus hampering the full assessment of long term efficacy and safety outcomes. The main concerns regard: - the lack of evidence on comparative outcomes of treatment with different drugs. The more relevant comparator is considered abiraterone and best supportive care. The indirect comparison with the results of the COU-AA-301 trial (abiraterone plus prednisone vs placebo plus prednisone) may be misleading. Indirect assessment and ranking of treatments that were not tested head-to-head and in population with different underlying characteristics should not be considered conclusive. - the early stopping of some trials precluded the definition of the actual survival benefit of enzalutamide All the trials were sponsored by the product manufactures.
Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: Monitor of PRES and seizure, signs and symptoms of ischemic heart disease is recommended.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable Comments: Enzalutamide is approved by the main regulatory agencies, including: • European Medical Agency (European Union) • Food and Drug Administration (United States) • Health Canada • Therapeutic Goods Administration (Australia) • Medsafe (New Zealand) • NPMA (China) • MHLW (Japan) Both in the European Union and in the US, enzalutamide is indicated as first-line therapy for the treatment of adult patients with metastatic CRPC who have not received chemotherapy or who have previously received docetaxel. Enzalutamide is also indicated for the treatment of non-metastatic CRPC. The drug received a standard approval (not accelerated) based on a randomized trial that showed improved metastasis-free survival (MFS), a novel surrogate end point. While surrogate endpoints may speed the approval of some efficacious drugs in this disease setting, they may lead to the approval of marginally (in)effective agents. MFS surrogacy for OS was demonstrated in 2011 but the standard of care in this setting improved substantially in last years: as outcomes in metastatic cancer improve, the

	use of tenuous surrogate end points for drug approval carries the risk of overtreatment and commitment to an indefinite duration of therapy with considerable adverse effects (Parikh 2018). Enzalutamide is also approved for the treatment of adult men with metastatic hormone-sensitive prostate cancer in combination with androgen deprivation therapy.
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: Enzalutamide is considered by Medicines Patent Pool Report for accessibility (Medicine Patent Pool). Medicines Patent Pool (MPP) is a United Nations-backed public health organisation working to increase access to, and facilitate the development of, life-saving medicines for low- and middle-income countries (LMICs). The report estimated that 168,000 people in countries in past MPP licences are guideline-eligible for treatment with enzalutamide. It concluded that enzalutamide, if available at more affordable prices, could offer some benefits to people with prostate cancer in LMICs. Enzalutamide has primary patent protection until 2026/2027 in some LMICs and could potentially be a candidate for MPP licensing, pending future recommendations by the EML cancer working group and the WHO Expert Committee.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Most cost effectiveness analyses on the role of enzalutamide in metastatic CRPC concluded that enzalutamide is a cost-effective alternative treatment after progression on docetaxel. However, cost analyses presented in the Application report conflicted conclusions depending on assumptions and health system context. All the studies refer to the price of the originator enzalutamide. With the introduction of generics price is expected to decrease but the actual impact is difficult to assess as it is not clear which countries have currently access to these generics. The Expert committee should carefully consider whether the recommendation of enzalutamide in the Model List could possibly have a positive impact in boosting the availability in LMICs. The Applicant anticipates that API costs will decline over time, in line with prices for tamoxifen, capecitabine and prednisolone. A decline of that magnitude would result in API costs of $0.012 to $0.036 per 40mg capsule, or $0.048 to $0.144 per day for enzalutamide. However, the rational or sources of information supporting this statement is not fully clear in the Application.

Any additional comments	A request for inclusion of enzalutamide in the Model list was submitted in 2017, while no Application was submitted for abiraterone. The Expert Committee's report recommended that enzalutamide should not be added at that time, but could be considered as part of a comprehensive review encompassing additional medicines (e.g. abiraterone). A request for inclusion of abiraterone and enzalutamide in the Model List was submitted in 2019. The Committee recommended abiraterone, but not enzalutamide, on the basis of its potential advantages in terms of emerging dosing strategies, lower pill burden and availability of generics, which would be associated with cost savings compared to similarly effective enzalutamide. "While enzalutamide remains an effective therapeutic option for mCRPC, its use instead of abiraterone could result in considerable additional expenditure at country level, without additional clinical benefit." Given the availability of abiraterone as first line treatment for metastatic CRPC, enzalutamide should clearly demonstrate its added value in terms of clinical outcomes. In case of similar effectiveness, a better cost effectiveness profile could support its inclusion. It should be noted that the WHO technical unit advised that it did not support the inclusion of abiraterone or enzalutamide on the Model List for management of CRPC though noting with interest ongoing studies and more mature data that may demonstrate significant benefit, particularly for OS. Compared to the Application of 2019, the current Application did not provide substantial new data. The ENZAMET study is now included but it regards hormone-sensitive prostate cancer. This open label trial suggested a benefit of enzalutamide over standard nonsteroidal antiandrogen drugs (bicalutamide, nilutamide, or flutamide) in terms of OS and PFS.
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	Although the benefit risk ratio was judged positive, this Reviewer still have concerns in relation to the listing proposal: 1) data on OS suggest a benefit but given the lack of comparison with alternative treatments already recommended in the Model List, it is difficult to conclude on the added value of the inclusion of enzalutamide. 2) additional costs compared to alternative treatments already recommended in the Model List remain an issue, as the impact of generic availability is not fully established.
References (if required)	Dawson NA, Leger P. Overview of the treatment of castration-resistant prostate cancer (CRPC) UpToDate, April 2021. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries CA CANCER J CLIN 2021;71:209–249. Khalaf DJ, Annala M, Taavitsainen S. Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial. Lancet Oncol 2019; 20: 1730–39. Sathianathen NJ, Oestreich MC, Brown SJ, et al. Abiraterone acetate in combination with androgen deprivation therapy compared to androgen deprivation therapy only for metastatic hormone-sensitive prostate cancer. Cochrane Database of Systematic Reviews Review 2020. Parikh RB, Prasad V. Metastasis-Free Survival in Prostate Cancer: Faster Drug

	Approvals, Better Drugs? J Clin Oncol. 2019 1;37(4):266-268. PROSPER Hussain M, Fizazi K, Saad F, et al: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 378:2465-2474, 2018 Pereira-Salgado A, Kwan EM, Tran B. et al. Systematic Review of Efficacy and Health Economic Implications of Real-world Treatment Sequencing in Prostate Cancer: Where Do the Newer Agents Enzalutamide and Abiraterone Fit in? Eur Urol Focus 2020 6;S2405-4569(20)30074-2. Medicine Patent Pool. Exploring the expansion of the medicine patent pool's mandate to patented essential medicines. Chapter 6 - Patented medicines for which the WHO Expert Committee recommended a therapeutic area review by a separate working group: Case studies on lung cancer, prostate cancer, multiple myeloma and breast cancer https://medicinespatentpool.org/uploads/2020/04/Chapter-6-Patented-medicines-for-which-the-WHO-Expert-Committee-recommended-a-therapeutic-area-review-by-a-separate-working-group-Case-studies-on-lung-cancer-prostate-cancer-multiple-myeloma-and-breast-cancer.pdf Mori K, Miura N, Mostafaei H, et al. Sequential therapy of abiraterone and enzalutamide in castration-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2020 Dec;23(4):539-548. Parker C, Castro E, Fizazi K, etal. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2020, 31, 9. https://doi.org/10.1016/j.annonc.2020.06.011