Clinical Effectiveness, Safety, Benefit-Harm Balance and Health Economic Characteristics of Treatments for Newly Diagnosed Metastatic Hormone-Sensitive Prostate Cancer

Report of the Appraisal Committee of the Swiss Medical Board

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Table of Contents

EXECUTIVE SUMMARY **5**

ABBREVIATIONS **7**

DEFINITIONS **10**

1. BACKGROUND **11**

2. METHODS **11**

3. RESULTS OF THE APPRAISAL **13**

3.1 EVIDENCE OF CLINICAL EFFECTIVENESS AND HARM 13

3.1.1 Desirable effects *14*

3.1.2 Undesirable effects *17*

3.1.3 Certainty of evidence *18*

3.1.4 Stakeholder Values *21*

3.1.5 Balance between desirable and undesirable effects *21*

3.2 CONSIDERATIONS REGARDING RESOURCE REQUIREMENTS AND COST-EFFECTIVENESS 23

3.2.1 Evidence *23*

3.2.2 Certainty of evidence with regard to resource requirements *26*

3.3 HEALTH EQUITY 28

3.4 ACCEPTABILITY 28

3.5 FEASIBILITY 28

4 RECOMMENDATIONS **29**

5 REFERENCES **30**

Executive Summary

Prostate cancer is the most frequent cancer in men and progresses relatively slowly, especially when detected and treated early. The mortality rate however remains relatively high compared to other cancers in Switzerland. Prostate cancer is typically hormone sensitive and unless cure is achieved through local therapy, the standard of care has been the use of androgen deprivation therapy (ADT). Metastatic hormone-sensitive prostate cancer (mHSPC) may be diagnosed *de novo* or occur after prior local therapy. Multiple novel therapeutic options have been introduced for mHSPC, including systemic chemotherapy (docetaxel), or second generation non-steroidal anti-androgen therapies (abiraterone, enzalutamide, apalutamide) and/or radiotherapy, which may be added to ADT. The optimal treatment strategy, however, remains unclear.

The Swiss Medical Board assessed whether the addition of these novel systemic therapies or radiation to ADT in men with newly diagnosed mHSPC, who had not previously undergone systemic therapy, is associated with better patient-relevant outcomes and is cost-effective compared to ADT alone, and whether one of the novel therapeutic strategies is superior to another. The assessment was based on standard methods for systematic reviews and health economic analysis. Based on this assessment, the present Appraisal Report was drafted using the Evidence-to-Decision (EtD) framework.

A network meta-analysis was conducted of 8 randomized, controlled trials (RCTs) to assess the effects of the novel systemic therapies in addition to ADT, compared to ADT alone and to each other. A pair-wise meta-analysis was conducted to assess the effects of radiotherapy + ADT compared to ADT alone. Clinical effectiveness assessment showed that all systemic therapies were effective in improving survival. The survival benefit of ADT + radiotherapy was limited to patients with low-volume *de novo* mHSPC. Although there was no statistically significant benefit of one systemic therapy over another, the novel hormonal treatments tended to have a higher survival rate, and had a statistically significantly larger effect on progression-free survival (PFS) compared to ADT + docetaxel. The evidence regarding health-related quality of life (HRQoL) indicated a benefit primarily for ADT + abiraterone, and a short-term HRQoL decline followed by improved preservation of longer-term HRQoL for ADT + docetaxel. No consistent difference in HRQoL was observed for ADT + enzalutamide or ADT + apalutamide. An overall statistically significant increase in any grade adverse event (AE) was observed for ADT + docetaxel compared to ADT over the short term. The overall incidence of any grade AEs for the other therapies was similar, although with some variability over time.

The Appraisal Committee concluded that the desirable effects were moderate and the differences in undesirable effects were variable. The level of evidence was considered moderate, given variable quality of evidence across studies, impacted by subject numbers, duration of follow-up and variability of control-group comparators. Reporting of HRQoL and AEs was inconsistent across studies and not available for some therapies. The Appraisal Committee concluded that the balance between desirable and undesirable effects favored the additional therapies although the balance varies across therapies.

The health economic analysis included a systematic review, *de novo* cost analysis and a budget impact analysis from the Swiss healthcare payer's perspective. Despite the high heterogeneity of the data, the results suggest that ADT + docetaxel may be cost-effective compared to ADT and this

strategy dominates the other systemic therapies. The Appraisal Committee determined that the cost-effectiveness of the systemic strategies varies, and that the budget impact would be small if all patients received docetaxel + ADT and would be large if all patients received a novel hormonal therapy + ADT.

The Appraisal Committee concluded that there may be important variability in the value given to the addition of systemic therapies or radiotherapy to ADT by different stakeholders. There was no major concern with respect to health equity. The Appraisal Committee deemed the addition of novel systemic therapies and/or radiotherapy to be both acceptable and feasible in Switzerland. Based on the evidence available, the Appraisal Committee issued a conditional recommendation in favor of the addition of novel systemic therapies and/or radiotherapy in men with newly diagnosed mHSPC who had not undergone prior systemic therapy.

Summary of judgments:

	Judgment	**Comment**
Desirable effects	Moderate	Some variation in effectiveness in low disease volume, prior local therapy, *de novo* subgroups , progression free survival and HRQoL
Undesirable effects	Variable	Grade and duration of undesirable effects are variable across therapies
Certainty of evidence	Moderate	GRADE assessment variable across studies/therapies
Stakeholder values	Possibly important variability	No data
Balance between desirable und undesirable effects	Favours therapy	Nett balance is variable across therapies
Resources required	Small for docetaxel, large for novel hormonal therapies	
Certainty of evidence of required resources	High	
Cost effectiveness	Varies	Docetaxel is cost effective. Novel hormonal therapies are dominated by docetaxel at current pricing levels
Equity	Probably no impact	No data
Acceptability	Acceptable	Used in practice
Feasibility	Feasible	Used in practice
RECOMMENDATION	Conditional recommendation in favour of therapies in addition to ADT	Some therapies have superior clinical effects in specific subgroups, one therapy (Docetaxel) is significantly more cost-effective at current prices, but associated with more adverse events and non-significantly inferior outcomes overall

ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AE	Adverse Effect
CBA	Cost-Benefit Analysis
BFI - SF	Brief Fatigue Inventory – Short Form
BHA	Benefit harm assessment
BIA	Budget impact analysis
bPFS	biochemical PFS: time to progression in biochemical markers
BPI	Brief Pain Inventory
CEAC	Cost-Effectiveness Acceptability Curve
CENTRAL	Cochrane Central Register of Controlled Trials
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHF	Swiss Franc
CI	Confidence Interval
CHOP	Swiss classification of surgeries
CRPC	Castration-Resistant Prostate Cancer
CT	Computed Tomography
DRG	Diagnosis Related Group
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
e.g.	exempli gratia (lat., = for example)
EQ-5D-5L	EuroQoL 5-Dimension 5-Level Questionnaire
FFS	Failure-Free Survival
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GDP	Gross Domestic Product
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICD	International Classification of Diseases
ICER	Incremental Cost-Effectiveness Ratio
i.e.	id est (lat., = that is)
IPD	Individual Patient Data
IQR	Interquartile Range
IRR	Incidence Rate Ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research

ITT	Intention-to-treat
i.v.	intravenous
KM	Kaplan-Meier
KVG	Swiss health insurance law (“Krankenversicherungsgesetz”)
LCL	Lower Confidence Limit
LHRH	Luteinizing Hormone-Releasing Hormone
LSMD	Least-Squares Mean Difference
LYs	Life Years
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MD	Mean Difference
mHSPC	Metastatic Hormone-Sensitive Prostate Cancer
MID	Minimal Important Difference
NMA	Network metaanalysis
nsAA	Non-Steroidal Anti-Androgens
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
bPFS	Biochemical Progression-Free Survival
cPFS	Clinical Progression-Free Survival
rPFS	Radiographic Progression-Free Survival
PH	Proportional Hazard
PICO	Population, Intervention, Comparator, Outcome
p.o.	per os (taken orally)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Risk Ratio
RT	Radiotherapy
sc.	Subcutaneous
SD	Standard Deviation
SFOPH	Swiss Federal Office of Public Health
SF-36	Short-Form-36 Questionnaire
SHS	Swiss Hospital Statistics
SFSO	Swiss Federal Statistical Office

SwissDRG	Swiss Diagnosis Related Group
UCL	Upper Confidence Limit
UK	United Kingdom
USA	United States of America
USD	United States Dollars
VAS	Visual Analogue Scale
vs.	versus
WTP	Willingness To Pay

DEFINITIONS

EQ-5D (https://euroqol.org)

EQ-5D VAS – Visual analog scale

EQ-5D-5L – 5 levels, includes Mobility, Self care, Usual Activities, Pain/Discomfort, Anxiety/Depression

SF-36 – Short Form Survey 36 (https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form.html)

EORTC QLQ-C30 – assesses quality of life of people with cancer

Functional Assessment of Cancer Therapy (https://www.facit.org/facit-measures-searchable-library)

FACT-G - Functional Assessment of Cancer Therapy -general

FACT-P - Functional Assessment of Cancer Therapy – Prostate (FACT-P)

FACIT-F - Functional Assessment of Chronic Illness Therapy – Fatigue

FACT-T -Functional Assessment of Cancer Therapy – Taxane (FACT-Taxane) e.g. decetaxel

Median time to pain interference progression: defined as the time from randomisation to the first increase by one half the standard deviation of baseline scores from baseline in the combined scale of items 9A–G from the BPI-SF)

Average pain progression: defined as the time from randomisation to first increase by 30% or more in average pain compared with baseline, as determined by the average of BPI-SF items 3–6

Dominated strategy (in CEA): Strategy with higher costs and lower QALYs

First generation nsAAs: bicalutamide, flutamide or nilutamide

Second generation nsAAs (novel hormonal therapies): abiraterone, enzalutamide, and apalutamide

ADT may involve orchidectomy or treatment with gonadotropin-releasing hormone agonists or antagonists

High volume disease (according to CHAARTED): defined as either of the following two criteria: visceral metastases or ≥4 bone lesions with ≥1 outside of the vertebral bodies and pelvis)

High risk disease: Gleason score ≥8 and/or ≥3 lesions on bone scan and/or presence of measurable visceral lesions [1]

NMA: Network meta-analysis compared three or more interventions simultaneously in one analysis by combining both direct evidence (of relative effects form within one study) and indirect evidence (of relative effects from different studies) evidence across a network of studies.[2]

Transitivity: applies to the validity of an indirect comparisons of treatment effects of different interventions across different randomized trial datasets where these effects are not directly compared are on average similar in all other relevant factors.[2]

P-score analyses: The P-score shows the probability of a treatment being the best treatment, derived from the posterior distributions of all treatment estimates.

1. BACKGROUND

Prostate cancer is the most frequent cancer in men, currently estimated to affect over 43,000 men in Switzerland[3]. Prostate cancer progresses fairly slowly, especially when detected and treated early, but despite the relatively high 5-year survival of 88.6% after diagnosis, the mortality rate of 22.0/100,000 person-years is still high compared to other cancer types[3].

Prostate cancer may be localized or metastatic (*de novo metastatic)* at the time of diagnosis (Figure 1). If localized, therapy may have curative or non-curative intent. Prostate cancer is typically hormone sensitive, i.e. androgen-dependent, and responds well to androgen deprivation therapy [ADT], which includes orchidectomy (i.e., surgical castration) or gonadotropin-releasing hormone agonists or antagonists (e.g. leuprolide, goserelin, degarelix, i.e.medical castration here)[4]. Patients with hormone-sensitive disease may either have ongoing sensitivity to ADT if responding to ADT treatment, or may be treatment naïve, without having had prior exposure to ADT. Approximately 20 – 40% of patients with prostate cancer will develop recurrence[4].

The management of metastatic, hormone-sensitive prostate cancer (mHSPC), diagnosed either *de novo* or having progressed after prior local therapy (Figure 1)*,* is currently a subject of high scientific and clinical interest [5-7]. Patients with *de novo* metastatic disease may have more aggressive cancers than those with metastasis occurring after prior therapy[4]. Data from the Swiss National Institute for Cancer Epidemiology and Registration[3], suggest that among patients with mHSPC, around 10% are diagnosed *de novo*, and 90% after disease progression[3]. The incidence and prevalence of mHSPC in Switzerland are not currently publicly available.

Treatment options for mHSPC currently involve ADT alone, which has long been the standard of care, or ADT in combination with chemotherapy (docetaxel), novel second generation anti-hormonal therapies (abiraterone – blocks androgen biosynthesis; enzalutamide or apalutamide – androgen receptor antagonists), and/or radiotherapy (Figure 1)[1,5,6,8-22]. These second generation non-steroidal antiandrogens (nsAAs) deliver more complete androgen blockade and have superseded the first generation nsAAs which have limited benefits[23,24]. The systemic therapies, docetaxel, abiraterone, enzalutamide and apalutamide differ in terms of effects on survival, disease progression, health-related quality of life (HRQoL), risk and severity of adverse events (AEs), patient acceptability, as well as cost. In addition, the clinical benefit of these agents may differ depending on disease volume and risk category, or whether mHSPC is diagnosed *de novo* or develops after prior local therapy. Current guidelines/expert opinion for mHPSC does not recommend a particular systemic mHSPC treatment[25,26]. The optimal treatment for men with mHSPC diagnosed *de novo* or with mHSPC occurring after prior local therapy therefore remains unclear.

To provide a basis for practice and policy recommendations in Switzerland this Health Technology Assessment (HTA) was conducted to evaluate the clinical effectiveness, safety, benefit-harm balance and health economic impact of the addition of docetaxel, abiraterone, enzalutamide, apalutamide and/or radiotherapy to ADT in men with mHSPC who had not previously undergone such systemic therapy, when compared to ADT alone and to each other.

2. METHODS

In the formal scoping process, the PICO (population, intervention, comparison, outcome) questions were defined in consultation with stakeholders. Evidence of clinical effectiveness and safety as well

as health economic evidence were assessed using the methods described in detail in the corresponding Assessment Report.

First, to assess clinical efficacy and safety, a network meta-analysis of 8 randomized controlled trials (RCTs) was conducted to determine the effects of the different additional mHSPC treatments compared to ADT alone and relative to each other. A separate pairwise meta-analysis was conducted of 2 RCTs to assess the effects of radiotherapy, as this treatment choice is independent of the choice of systemic treatment, and is only indicated in *de novo* mHSPC. Clinical outcomes of interest included overall survival (OS), HRQoL, progression-free survival (PFS) and AEs. Clinical effectiveness was stratified by sub-group where possible, including high- vs. low-volume disease, *de novo* mHPSC vs. progression after prior local therapy, restricted vs. unrestricted performance status. Health economic outcomes included costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs) and a budget impact analysis (BIA).

The population of interest included adult men with newly diagnosed mHSPC – either *de novo* or having progressed after prior local therapy – who had not previously undergone systemic therapy. Patients were variably recruited for periods between 2004 and 2017. Median follow-up across the RCTs ranged from 14.4 months to 83.9 months, sample sizes ranged between 385 to 2061 participants, and mean subject age ranged from 63 to 70 years. One study included patients from Switzerland.

The interventions of interest included the following:

- ADT + docetaxel (75mg/m2 body surface area, administered i.v. every 3 weeks for 6 cycles) + prednisone 10mg/day during 6 cycles, followed by ADT alone
- ADT + abiraterone acetate (1,000mg/day p.o.) + prednisone 5mg/day until disease progression
- ADT+ enzalutamide (160mg/day p.o.) until disease progression
- ADT+ apalutamide (240mg/day p.o.) until disease progression
- ADT + radiotherapy (external beam radiation therapy to the prostate administered in various doses and frequencies, followed by ADT alone).

The following comparator treatments were considered:

- ADT alone or in combination with placebo, daily oral medication (licensed dose)
- ADT + first-generation nsAA (such as bicalutamide, flutamide or nilutamide) alone or in combination with placebo, daily oral medication (licensed dose).

Second, in addition to analysis of AEs reported in the included RCTS, a novel Benefit-Harm Assessment (BHA) was performed to evaluate the relative effects of each therapy over a time horizon of 24 months. The methods applied are described in detail in the Assessment Report. This time horizon corresponded to the median progression-free survival of mHSPC patients based on the pooled estimate from the RCTs included in the economic evaluation within this HTA. Given the novelty of this approach and that BHA has not thus far been incorporated into the HTAs completed by the Swiss Medical Board, the BHA results are briefly described here but were not included in the final assessment. AEs were graded as follows: grade 1 -mild, grade 2 - moderate, grade 3 - severe, grade 4 – life-threatening, grade 5 – death.

Third, the health economic assessment comprised a systematic health economic literature review, a cost effectiveness analysis (CEA) and a budget impact analysis (BIA). Detailed methods and assumptions are outlined in the corresponding Health Economic Assessment Report. The adopted perspectives, time horizons, and types of costs considered in the analyses were heterogeneous. No study included data from Switzerland. No data was available for enzalutamide, apalutamide or radiotherapy. The CEA analysed the cost-effectiveness of ADT and the four ADT combination strategies (ADT with docetaxel, abiraterone, enzalutamide, or apalutamide) from a Swiss healthcare payer perspective, over a 15-year time horizon. Radiation therapy was not included. Drug, inpatient and outpatient costs were drawn from official and publicly available Swiss sources. Two Swiss medical experts were consulted to verify or obtain resource use values and assumptions appropriate for Switzerland. For the BIA, estimates of eligible patients were extrapolated from national data on prostate cancer incidence and prevalence, combined with internationally published information. Costs at the national level were estimated from the Swiss healthcare payer perspective until 2030. Given lack of data on the proportion of eligible patients with mHSPC in Switzerland receiving the interventions of interest, and since the market access of the investigated treatments occurred in different years, varying proportional treatment distributions were analysed, assuming that patients would not switch between different treatment strategies.

The Appraisal Committee discussed the results of the assessment in a meeting held in August 2021 using the Evidence-to-Decision (EtD) framework[27]. Recommendations were formulated based on the available evidence and additional considerations including feedback from stakeholders. All recommendations apply to the addition of systemic therapies or radiation to the current standard of care, ADT, in the population of interest: adult men with newly diagnosed mHSPC– either *de novo* or having progressed after prior local therapy – who had not previously undergone systemic therapy. The EtD framework considers several domains such as the balance between desirable and undesirable effects, quality of evidence, cost-utility/resource requirements, patient values, health equity, and acceptability/feasibility of the intervention. Differences in desirable and undesirable effects were categorized as large, moderate, small, or trivial. The resulting recommendations were formulated as 'strong' or 'conditional' in favor of a given intervention, in favor of either the intervention or comparator, or against the intervention. Recommendations were supplemented by considerations regarding subgroups, implementation aspects, monitoring and evaluation, and research priorities.

3. RESULTS OF THE APPRAISAL

3.1 Evidence of clinical effectiveness and harm

Of the eight RCTs included in systematic review and network meta-analysis (Figure 2), three RCTs evaluated ADT + docetaxel [GETUG-AFU 15[17,18], n = 385; CHAARTED[8,22], n = 790; STAMPEDE arm C [16,21], n= 1086], two each evaluated ADT + abiraterone [LATITUDE[1,10], n = 1199; STAMPEDE arm G[19,20], n = 901], ADT + enzalutamide [ENZAMET[9], n = 1125; ARCHES[12], n = 1150] and ADT + radiotherapy [STAMPEDE arm H[11], n = 2061; HORRAD[13], n = 432], and one evaluated ADT + apalutamide [TITAN[14,15], n = 1052]. LATITUDE included only high-risk patients. ENZAMET allowed the concurrent use of docetaxel and used a combination of ADT + nsAA as the comparator intervention. STAMPEDE also included pateints with high-risk non-metastatic disease, with data for patients with metastatic

disease not always separately reported. Results from the NMA were reported as hazard ratios [HR] with 95% confidence intervals (CI).

3.1.1 Desirable effects

3.1.1.1 Evidence from randomized studies

Overall survival:

For the primary outcome of *overall survival*, in the NMA all systemic mHSPC treatments showed a statistically significant advantage over ADT alone, with individual HRs (for reduced likelihood of death) of 0.77 (95% CI 0.69 to 0.85; p<0.001) for ADT + docetaxel, 0.66 (95% CI 0.58 to 0.74; p<0.001) for ADT + abiraterone, 0.63 (95% CI 0.48 to 0.83; p<0.001) for ADT + enzalutamide, and 0.65 (95% CI 0.53 to 0.79; p<0.001) for ADT + apalutamide (Table 1). None of the comparisons between the different interventions showed a statistically significant survival advantage of one systemic mHSPC treatment over another. Regarding the ranking of the different systemic mHSPC treatments in terms of survival advantage, the P-Score analysis resulted in the highest P-Score for ADT+ enzalutamide (0.77) followed by ADT+ apalutamide (0.72), ADT+ abiraterone (0.71), ADT+ docetaxel (0.3) and ADT (< 0.001). In sensitivity analyses, however there was considerable uncertainty regarding the evidence from ENZAMET due to the use of ADT + nsAA in the comparator group, and that the risk of death in patients not receiving docetaxel was much lower than that reported in other studies. When EZAMET was excluded, the P-Score ranking changed, being highest for ADT+ abiraterone (0.82) followed by ADT+ apalutamide (0.82), ADT + docetaxel (0.43), ADT+ enzalutamide (0.4) and ADT (< 0.04). In the pairwise meta-analysis for ADT + radiotherapy compared to ADT alone, there was no statistically significant benefit on survival in the overall mHSPC population (HR 0.91; 95% CI 0.92 to 1.03; p=0.15).

Subgroup analyses:

Seven studies were included in the *high vs. low disease volume subgroup* analysis for overall survival: three for ADT + docetaxel[16,17,22], two for ADT + abiraterone[10,19], and one each for ADT + enzalutamide[9] and ADT + apalutamide[15], all were compared to ADT alone (Table 1). Among subjects with low volume disease, a statistically significant survival benefit over ADT alone was found for all novel hormonal treatments (all p ≤ 0.009), but not for docetaxel (p=0.38). In subjects with high volume disease, all systemic combination treatments showed a statistically significant survival benefit over ADT alone (all p ≤ 0.049). A survival benefit from ADT + radiotherapy was only observed on the low volume *de novo* mHSPC subgroup (p = 0.002).

Five studies were included in the *de novo mHSPC subgroup* analysis: three providing evidence for ADT + docetaxel[16,17,22], two for ADT + abiraterone[10,19] and one for ADT + apalutamide[15], all compared to ADT alone (Table 1). ENZAMET was excluded. A statistically significant survival benefit was found for all three systemic treatments compared with ADT alone (all p < 0.001). ADT + radiotherapy was analyzed in two studies[11,13] where overall no significant survival benefit was found (p=0.15).

Four studies provided data on subjects with mHSPC who had *progressed after prior local therapy*: two for ADT + docetaxel[17,22], one for ADT + abiraterone[19,20], and one for ADT + apalutamide[15], all compared to ADT alone (Table 1). ENZAMET was excluded. A statistically significant survival benefit

was only evident for ADT + apalutamide vs ADT alone (p=0.001) No studies evaluated radiotherapy in subjects who had undergone prior local therapy.

Five studies reported data for the *Eastern Cooperative Oncology Group (ECOG) performance status subgroups*: three studies on ADT + docetaxel[16,17,22], two studies on ADT + abiraterone[1,20] and one study on ADT + apalutamide[15]. All systemic therapies were found to have statistically significant survival benefits in the ECOG 0 subgroup (all $p \leq 0.005$) and the ECOG ≥ 1 subgroups (all $p \leq 0.002$) compared to ADT alone (Table 1). No survival benefit was found for ADT + radiotherapy in either ECOG subgroup.

Overall, in the assessment of clinical efficacy, docetaxel, abiraterone, enzalutamide, and apalutamide in combination with ADT all confer a relevant survival benefit in patients with newly diagnosed mHSPC compared to ADT alone. None of the systemic combination treatments was superior to the others in prolonging survival overall. In subgroup analyses, a statistically significant survival benefit was observed for all novel hormonal treatments, but not for ADT + docetaxel in the low-volume subgroup. All systemic combination treatments conferred a statistically significant survival benefit over ADT alone in the high-volume and the de novo diagnosed mHSPC subgroups. ADT + apalutamide was the only therapy with a significant effect in the subgroup who had undergone prior local therapy. ADT + radiotherapy provided a statistically significant benefit in low-volume, but not in high-volume de novo mHSPC.

Health Related Quality of Life

Information on HRQoL was reported in seven studies: three with ADT + Docetaxel[GETUG-AFU 15[18], CHAARTED[28], STAMPEDE[29]], two with ADT + Abiraterone[LATITUDE[30], STAMPEDE[29]], two with enzalutamide [ENZAMET[31], ARCHES[12]] and two with apalutamide [TITAN[14,32]]. Details of HRQoL are outlined in Table 5 of the corresponding Assessment Report. There was significant heterogeneity in the instruments used, evaluation, analysis and presentation of specific HRQoL-related endpoints between publications. No meta-analysis was possible based on the data available, therefore a narrative review was performed. Subgroup analysis was only conducted in one study evaluating ADT + docetaxel vs. ADT, examining disease volume subgroups. No data on HRQoL was available for treatment with ADT + radiotherapy.

Overall, ADT + docetaxel compared with ADT alone was associated with relatively consistently lower HRQoL and higher fatigue scores over the first 3-6 months of treatment (attributable to the acute effects of chemotherapy, all $p \leq 0.005$). Scores at 12 months were not different. Specifically, the mean global EORTC QLQ-C30 was significantly lower at 3 and 6 months for ADT + docetaxel vs ADT alone (all $p < 0.005$), driven by differences in the physical function and fatigue subscales. Although the FACT-P mean global score was not statistically significantly different between treatment groups, the FACT-P scores for physical well-being, functional well-being and trial outcome index subscales were statistically significantly lower in the ADT + docetaxel group, but only at 3 months ($p = 0.009$). Subjects randomized to ADT + docetaxel appeared to experience a short-term deterioration in FACT-P scores, while those assigned to ADT alone appeared to experience a protracted deterioration in FACT-P beyond 3 months of follow-up (all $p \leq 0.01$). In the single study[28] that stratified by disease volume, the deterioration in FACT-P scores observed in those randomized to ADT+ Docetaxel at 3 months, and at later time points in those randomized to ADT, was only significant in the low-volume

groups (p = 0.003). Overall, the ADT + docetaxel group also scored lower in FACIT-F fatigue scores (p<0.001) at 3 months and FACT-T at all follow-up time points compared to subjects randomized to ADT alone (all p ≤ 0.03). BPI-SF scores were not statistically significant different between groups.

One study[30] found significant benefit for ADT + abiraterone compared with ADT alone for the FACT-P, BPI-SF, BFI-F, EQ-5D VAS and EQ-5D-5L scores for fatigue, pain, health status and well-being up to 2.5 years. There was no difference in FACT-G subscales for general, emotional, function and social wellbeing. In another study[29] comparing ADT + abiraterone with ADT + docetaxel, HRQoL, measured by average global EORTC QLQ-C30 scores, was significantly better in the abiraterone group at 3 (p = 0.001) and 6 months (p < 0.001), but not at 1 or 2 years (all p ≥ 0.051).

In one study[31] a significant benefit of ADT + enzalutamide over ADT + nsAA was observed from week 4 to week 156 , as reflected in the EORTC QLQ-C30 subscales for fatigue (p < 0.0001), cognitive functioning (p<0.001) and physical functioning (p<0.0002), although overall scores were not different (p=0.16). In a second study[12] FACT-P scores were not different over 2 years between subjects randomized to ADT + enzalutamide vs. ADT alone.

HRQoL as measured by FACT-P, BPI-SF, BFI-F and EQ-5D-5L over almost 2 years were not found to be significantly different between subject randomized to ADT + apalutamide compared to ADT alone. Pain scores tended to be higher in the ADT alone group and fatigue tended to be higher in the ADT + apalutamide group, although neither reached statistical significance.

Taken together, the evidence related to HRQoL indicated a benefit primarily for ADT + abiraterone, and a short-term decline in HRQoL followed by improved preservation of longer-term HRQoL for ADT + docetaxel. No consistent difference in HRQoL was observed for ADT + enzalutamide or ADT + apalutamide.

Progression-Free Survival

Data on PFS was available in seven RCTS: three for ADT + docetaxel[16,17,22]; 2 for ADT + abiraterone[1,19]; 2 for ADT + Enzalutamide[9,12]; 1 for ADT + apalutamide[14]; all compared with ADT alone, and one for ADT + abiraterone vs. ADT + docetaxel[16,33]. In the pooled NMA, all systemic mHSPC treatments showed a statistically significant benefit on PFS in comparison to ADT alone (Table 1): ADT + docetaxel (HR 0.67, 95% CI 0.60 to 0.74; p<0.001), ADT + abiraterone (HR 0.46, 95% CI 0.41 to 0.52; p<0.001), ADT + enzalutamide (HR 0.36, 95% CI 0.30 to 0.44; p<0.001), and ADT + apalutamide (HR 0.49, 95% CI 0.39 to 0.62; p<0.001). Based on indirect evidence, ADT + abiraterone, ADT + enzalutamide and ADT + apalutamide were all statistically significantly superior to ADT + docetaxel for PFS (all p ≤ 0.02). None of the novel hormonal agents in combination with ADT was statistically significantly superior to another. No benefit on PFS was observed for ADT + radiotherapy compared to ADT alone (p=0.50), reported in a single study[11].

In summary, regarding PFS, a statistically significantly longer time to progression was observed for all systemic mHSPC treatments compared to ADT alone. Novel hormonal treatments were superior to ADT + docetaxel, but no significant difference was observed between the novel hormonal treatments. Radiotherapy did not prolong PFS.

3.1.1.2 Additional considerations

Pre-planned subgroup analyses for ***high vs. low risk disease*** were not conducted due to sparsity of stratified data reported in the relevant RCTs. Results for high and low *volume* disease groups were considered sufficiently indicative of the importance of disease burden for treatment decision making. This observation is consistent with statements from the recent Swiss consensus panel on advanced prostate cancer, where the majority of experts voted that distinguishing the two classifications (risk and volume) is not necessary for decision making regarding intensification of therapy for mHSPC in clinical practice[26]. While clinical practice guidelines currently recommend any of the systemic treatments in the mHSPC setting irrespective of disease burden, expert consensus increasingly suggests a preference for the novel hormonal therapies over docetaxel in the low-volume setting. The observed benefit of radiation being restricted to the low volume subgroup is in accordance with current practice guidelines, which recommend the use of radiotherapy in combination with ADT only in low-volume *de novo* mHSPC.

3.1.1.3 Judgment

The Appraisal Committee concluded that the desirable effects of the addition of systemic therapies and/or radiotherapy to ADT alone in the population of interest are moderate.

3.1.2 Undesirable effects

3.1.2.1 Evidence from randomized studies

All studies investigating systemic mHSPC treatments reported data on adverse events (AEs), although in varying degrees of detail. Older studies tended to report AEs in less detail and to focus on severe AEs. Incident rate ratios (IRR) were calculated for each therapy compared with ADT alone. The most important AEs were summarized narratively.

Three studies reported AEs for ADT + docetaxel compared with ADT alone [2 reported only grades 3 – 5[18,22], 1 reported grades 1 – 5[21]]. A significant IRR was observed for any grade AE for ADT + docetaxel (IRR 1.14; 95% CI 1.03 to 1.26; p=0.01), although when stratified by severity, the IRRs were not significant for either grades 1 -2 or grades 3 – 5 (both p=0.06). AEs were reported for ADT + abiraterone compared with ADT alone in 2 studies [1 reported grades 1 - 5[21], 1 reported grades 3 – 5[10]]. Overall there was no significant difference in IRR of AEs for ADT + abiraterone (IRR 1.01; 95% CI 0.94 to 1.09; p= 0.75). When stratified by AE severity, ADT + abiraterone was associated with a significantly lower IRR for grade 1-2 AEs vs. ADT (IRR 0.72; 95% CI 0.57 to 0.90; p=0.004) but a significantly higher IRR for grade 3-5 AEs vs. ADT (IRR 1.40; 95% CI 1.26 to 1.55; p<0.001). Two studies evaluated AEs with ADT + enzalutamide compared with ADT alone [both reported grades 1-5[9,12]]. Overall and when stratified by severity there was no statistically significant increase in the IRR of AEs with ADT + enzalutamide (overall IRR 1.01; 95% CI 0.92 to 1.10; p=0.90) Similarly, one study which evaluated the IRR of AEs with ADT + apalutamide [limited AE reporting[14]] also found no significant differences in IRR for AEs overall (IRR 1.00; 95% CI 0.88 to 1.13; p=0.98) or when stratified by grade severity. Analysis of AEs associated with ADT + radiotherapy compared with ADT alone [1 study[11]] found a similar incidence of grade 3-5 AEs between groups of 39% in the ADT + radiotherapy group and 38% in the ADT alone group.

Overall, a statistically significant increase in any grade AEs was observed for ADT + docetaxel compared to ADT alone, primarily driven by higher incidence rates of grade 3-5 AEs. For ADT + abiraterone, the incidence of grade 1-2 AEs was lower, but of grade 3-5 AEs was higher than for ADT alone, resulting in a similar incidence of any grade AEs. For both ADT + enzalutamide and ADT + apalutamide, no statistically significant difference in AE rates was observed versus ADT alone. Limited data was available for ADT + radiotherapy, which showed similar grade 3-5 AE rates as for ADT alone.

3.1.2.2 Additional considerations

Overall the spectrum, severity and duration of adverse events was very heterogeneous. The most frequent and/or clinically important AEs of any grade reported for ADT + docetaxel included alopecia, nail changes, hot flushes, diarrhoea, nausea/vomiting, peripheral oedema, peripheral sensory neuropathy, increased liver enzymes, fatigue, febrile neutropenia and stomatitis; for ADT + abiraterone were cerebrovascular disease, cardiovascular disease and cardiac failure, falls and fractures, hot flushes, diarrhoea, hypertension, fatigue, increased liver enzymes, hypokalaemia, rash and peripheral oedema; for ADT + enzalutamide were hot flushes, fatigue, hypertension, nausea/vomiting, cognitive disorder, diarrhoea, peripheral oedema, peripheral sensory neuropathy, falls and fractures, rash, cardiac arrhythmia, cardiovascular disease and seizures; for ADT + apalutamide included rash, hot flushes, fatigue, hypertension, falls and fractures, and seizures. Radiotherapy was specifically associated with acute toxic effects on bladder and bowel.

The absence of data on HRQoL and AEs by patient subgroup is an important limitation. Such data would be highly relevant for example for older patients or those with poorer baseline performance status who may be at higher risk of AEs or deterioration in HRQoL. It is also important to recognize that certain AEs can be alleviated (e.g. medication for hot flushes, osteoprotective treatment against fractures, cooling hat for docetaxel-induced alopecia, physical exercise for fatigue) and not all AEs are experienced similarly by all patients. Given the data available, the impact of AEs on HRQoL and daily activities could not be assessed in the systematic review.

3.1.2.3 Judgment

The Appraisal Committee concluded that the differences in undesirable effects between ADT alone or ADT in combination with each additional systemic therapy and/or radiotherapy in the population of interest were variable.

3.1.3 Certainty of evidence

<u>Overall survival</u>

All studies were judged to have a low risk of bias related to overall survival and PFS. Overall heterogeneity in the network was low (I2=0.0%). Heterogeneity between studies was low for treatment effects for ADT + docetaxel (I2=0.0%), ADT + abiraterone (I2=0.0%) and ADT + radiotherapy (I2=0.0%) compared with ADT. Heterogeneity was moderate between studies on

treatment effects of ADT + enzalutamide (I2=55.3%), given the considerable differences in effects on overall survival between ENZAMET (HR 0.53; 95% CI 0.37 to 0.75) and ARCHES (HR 0.81; 95% CI 0.53 to 1.24). There was important incoherence between direct and indirect effect estimates for survival benefit of ADT + abiraterone vs. ADT + docetaxel however, with direct evidence from STAMPEDE (HR 1.13; 95% CI 0.77 to 1.66; p=NS) showing survival benefit for ADT + docetaxel, in contrast to pooled data from 4 studies showing significant survival benefit for ADT + abiraterone (HR 0.81: 95% CI 0.68 to 0.96; p=0.02). With respect to analyses of ADT + Radiation, classification of disease volume across studies was not consistent.

GRADE Assessment for overall survival

The quality of the evidence for overall survival was judged to be high for the effects of ADT + docetaxel and ADT + apalutamide, moderate for ADT + abiraterone and ADT + radiotherapy, and low for ADT + enzalutamide, each compared with ADT alone. Direct and indirect estimates as well as NMA ratings for treatment comparisons are reported in Table 2.

Sensitivity analyses

Exclusion of ENZAMET led to relevant change in the treatment effect estimate for overall survival for ADT + enzalutamide compared to ADT alone, which was no longer statistically significant (HR 0.81; 95% CI 0.53 to 1.24; p=0.35).Exclusion of the LATITUDE trial did not relevantly affect the treatment effect estimate for ADT + abiraterone compared to ADT alone (HR 0.65; 95% CI 0.51 to 0.82; p<0.001). Exclusion of the evidence from a subgroup-analysis STAMPEDE[33] did not lead to a relevant change in the treatment effect estimates for ADT + docetaxel or ADT + abiraterone compared to ADT alone, but did lead to a statistically significant estimate for the effect of ADT + abiraterone compared to ADT + docetaxel (HR 0.81; 95% CI 0.68 to 0.96; p=0.02). Similar sensitivity analyses for PFS did not lead to any relevant change in effect estimates.

HRQoL

Data on HRQoL-related outcomes was reported less frequently and substantially less consistently than survival data across the included RCTs. There was large heterogeneity in the measurement, evaluation, analysis and presentation of specific HRQoL-related endpoints between publications. Evidence from 4 studies was judged to be at high overall risk of bias [GETUG-AFU 15[18], CHAARTED[28], ENZAMET[31], STAMPEDE[29]], evidence from 2 studies was judged to be at low risk of bias [LATITUDE[30], TITAN[14,32]] and some concerns existed in the remaining study although it was otherwise judged to be at low risk of bias [ARCHES[12]]. No data was available to assess the impact of Radiation on HRQoL. Data for subgroup analysis for HRQoL was only provided in one RCT, therefore no statement could be made regarding the potential benefit of the treatments on HRQoL in the different subgroups of interest.

Progression-free Survival

With regard to PFS, heterogeneity in the network was low. In various sensitivity analyses, exclusion of ENZAMET, LATITUDE, STAMPEDE or use of alternative effect estimates from ARCHES did not lead to any relevant change in the effect estimate for ADT + enzalutamide on PFS vs. ADT alone or for ADT + abiraterone vs. ADT alone.

AEs

Reporting of AEs was relatively inconsistent across studies, across time -periods and in duration of follow-up. Studies were not powered to evaluate differences in AE incidence rates. Studies on ADT + docetaxel and ADT + abiraterone reached higher precision and were therefore more likely to find a statistically significant difference. In addition, comparison between different treatments assumes that AE incidences are constant over time, which may bias against ADT + docetaxel which is a short-term therapy (6 months). No judgement was possible on AEs across subgroups.

Further important limitations of the analysis include variability of duration of follow up (range 14.4 to 83.9 months); despite statistical significance being reached in some analyses, the minimum important difference [MID] was not often reached questioning the true clinical relevance; robust stratification into clinical subgroups was limited.

3.1.3.1 Additional considerations

Important strengths of the systematic review include the following:

1. The findings are consistent with prior systematic reviews and meta-analyses on this topic
2. This systematic review provides more detail on HRQoL than prior studies
3. Multiple sensitivity analyses tend to confirm overall results
4. Overall, the included studies were judged to sufficiently fulfil the criteria for transitivity, with some reservations regarding ENZAMET.

Important limitations of the systematic review include the following issues:

1. Uncertainty about the appropriateness of inclusion of evidence from LATITUDE (included only high-risk de novo mHSPC patients), ENZAMET (comparator group different to other studies - ADT + nsAA, and docetaxel was used concurrently in a substantial proportion of subjects; baseline risk appeared lower among participants not receiving docetaxel) and STAMPEDE (also included non-metastatic patients; stratification by metastasis status only possible for overall survival analyses). After sensitivity analyses, considerable uncertainty remained about the applicability of estimates from ENZAMET.
2. Data from ARCHES on overall survival was considered immature at the time of publication, with a median follow-up of only 14.4 months.
3. In LATITUDE, patients were allowed to cross-over due to a protocol amendment after the first interim analysis, which could have led to an underestimation of the benefit of abiraterone on overall survival, PFS and HRQoL, although treatment estimates before and after the protocol amendment did not differ relevantly.
4. There was partial overlap of study participants in the different STAMPEDE trial arms and correlation estimates relied on multiple assumptions in the absence of individual-patient data. The choice of the correlation matrix was not found to influence the findings, however.
5. The distribution of subsequent treatments in patients after progression differed between studies and between intervention arms within studies and may have impacted outcomes. Available data did not permit robust analysis.
6. Five ongoing trials were identified that would have been eligible for the systematic review. Once published, these studies may further add to the findings presented in this report.

3.1.3.2 Judgment

The Appraisal Committee concluded that the overall certainty of evidence regarding the effects of systemic therapy and/or radiation with ADT in comparison to ADT alone, or to each other, in the population of interest was moderate.

3.1.4 Stakeholder Values

It would not be unreasonable to expect that the benefit of the novel therapies and radiotherapy on overall survival would be highly valued by most stakeholders. How this may be modified by the balance between impact on HRQoL and AEs, as their nature, severity and duration are not clear, and this may differ by individual therapy and be highly patient-specific.

For some men the symptoms resulting from castration associated with ADT alone may be unacceptable, and some choose to forgo this and rather "watch and wait". Others may be willing to accept short term AEs and a reduction in HRQoL associated with time-limited 6 cycle course of Docetaxel therapy given the chance of better preservation of HRQoL over the longer term, and potentially avoid life-long additional hormonal therapy. These patients may retain the option of future hormonal therapy should their disease progress. Other patients may choose the potentially lower risk of short-term AEs and preserved HRQoL associated with the novel hormonal therapies despite needing to take these therapies over the long term. Shared decision-making on an individual basis is therefore necessary given the absence of clear clinical superiority of one therapy over the other overall, but also given some potential superiority/inferiority of individual therapies in certain patient subgroups.

3.1.4.1 Additional considerations

Data reported in the RCTs was insufficient to reliably determine any subgroup differences which could be considerable. Data was not available regarding HRQoL for radiation.

3.1.4.2 Judgment

The Appraisal Committee concluded that there was possibly important variability in how stakeholders value the effects of the addition of systemic therapies or radiation to in the population of interest.

3.1.5 Balance between desirable and undesirable effects

Despite a clear survival advantage for the docetaxel and the novel second generation hormonal therapies overall, and for radiation in the low volume *de novo* subgroup of patents with mHSPC, the impact of AEs and on individual HRQoL remain unclear.

Among patients randomized to ADT + docetaxel vs. ADT alone the overall EORTC QLQ-C30 score differences met the threshold for an MID of 6 points at 3 and 6 months, but this was no longer significant at 12 months (67.6 ± 18.4 vs. 66.4 ± 20.2; p=0.70). Upon closer examination, the differences were only significant for the physical function and fatigue subscales. Similarly, the MID of ≥ 3 points for FACIT-F score and the MID of ≥ 1 point for the FACT-T score were met at 3 months. In

contrast, between-group differences in FACT-P and BPI-SF for ADT + docetaxel vs. ADT did not meet the threshold criteria for a MID. Overall, ADT + docetaxel was associated with a reduction in HRQoL among patients receiving ADT + docetaxel at 3-6 months compared to ADT alone, but not at later time points. There was some evidence that HRQoL may be maintained for longer in patients receiving ADT + docetaxel compared to those receiving ADT alone.

Among patients randomized to ADT + abiraterone vs. ADT alone, although statistically significant differences in multiple HRQ0L scores were observed, the median time to worst pain intensity, median time to pain interference progression, the average pain progression, median time to worst fatigue intensity and median time to fatigue interference progression were not reached in either study arm. However, the 25th percentile showed a significant difference in median time to worst fatigue intensity of 18.4 months (95% CI 21.9 to 27.7) with ADT + abiraterone and 6.5 months (95% CI 5.6 to 9.2) in the ADT group (HR 0.65; 95% CI 0.53 to 0.81). Similarly, the 25th percentiles showed a 41% risk reduction in median time to fatigue interference progression (HR 0.59; 95% CI 0.47 to 0.75) and a 15% risk reduction median time to deterioration of the FACT-P (HR 0.85; 95% CI 0.74 to 0.99) for ADT + Abiraterone compared with ADT alone. When compared with ADT + docetaxel, ADT + abiraterone was associated with significantly higher average global EORTC QLQ-C30 scores over 2 years, but this did not meet the MID threshold of 6 points.

Patients randomised to ADT + enzalutamide compared to ADT + nsAA had statistically significantly lower scores in various EORTC QLQ-C30 subscales from week 4 to 156 including for fatigue, cognitive functioning and for physical functioning, although global scores were not statistically significantly different between the ADT + enzalutamide and ADT + nsAA groups (LSMD 1.1; 95% CI -0.4 to 2.6; p=0.16). None of the differences in global or subscale scores exceeded the MID threshold of 6 to 10 points. However, estimated HRQoL-deterioration-free survival at 3 years favoured ADT + enzalutamide in terms of global HRQoL (32% vs. 18%, p<0.0001), cognitive functioning (33% vs. 21%, p=0.0003) and physical functioning (31% vs. 22%, p=0.001), but not fatigue (26% vs. 18%, p=0.10). When ADT + enzalutamide was compared to ADT alone however there were no differences in FACT-P scores over 2 years.

Among patients randomized to ADT + apalutamide vs. ADT alone there were no significant differences in multiple HRQoL scores. Patients in the ADT alone group however consistently reported non-significantly higher scores for worst pain intensity and pain interference in the BPI-SF. Conversely, patients receiving ADT + apalutamide generally reported non-significantly higher scores for worst fatigue intensity and fatigue interference in the BFI-F.

3.1.5.1 Additional considerations

In an attempt to objectively assess the relative benefits and harms, a formal BHA was conducted in addition to the systematic review. Details of this analysis are outlined in the corresponding Assessment Report. The benefit-harm balance of systemic mHSPC treatments was assessed from a clinical decision-making perspective using a 2-year time horizon. In this analysis, mHSPC patients treated with ADT + abiraterone, ADT + enzalutamide, and ADT + apalutamide demonstrated a net clinical benefit at 24 months compared to patients treated with ADT alone, whereas the benefits of ADT + docetaxel were less likely to outweigh the harms of treatment. This conclusion regarding docetaxel was not consistent with the findings of the systematic review or the cost-effectiveness

analyses. The unfavourable benefit-harm balance for ADT+ docetaxel in the BHA was mainly driven by the higher rates of AEs, which offset the benefit. Crucially important limitations in interpretation of this analysis must be considered: i) any AE was considered a harm, regardless of severity and consequence; ii) the BHA is strongly dependent on the evidence selection which for AE and HRQoL was heterogeneous across studies. Much more granular and consistently reported data is required; iii) thresholds for net clinical benefit and net harm were arbitrarily decided; iv) empirically determined preference weights from patient preference studies in mHSPC were not available for the specified outcomes therefore generic values from other disease contexts including breast cancer were used, with questionable relevance to prostate cancer; v) the investigators assigned preference weights to outcomes; vi) this analysis represents the first time that the approach by Gail et al.[34] has been applied to treatment for metastatic cancer (considers AEs over the long term in contrast to other methodologies which evaluate toxicities according to disease treatment/trajectory time partitions). Thus the most appropriate model for quantifying the benefit-harm balance is not known and is likely highly dependent on the context and choice of treatments; vii) subgroup analysis was not possible, which may be the most important contribution given the clinical heterogeneity of mHSPC; viii) radiation was not included

This assessment is among the first BHAs conducted in the context of mHSPC, and there is little evidence for comparison. Therefore, the results should be interpreted with caution and need to be considered in light of the significant limitations of the study, including the lack of detail of reported AE data (e.g., estimates for all different types and severity level of AEs), lack of representative outcome rates from observational studies, and lack of empirical preference weights from patient preference surveys. *The evidence from the BHA was therefore not considered for inclusion in the judgements in this HTA.* The Appraisal Committee however appreciates the potential value of such analyses to improve input for clinical decision-making.

3.1.5.2 Judgment

The Appraisal Committee concluded that the balance of desirable and undesirable effects overall favours systemic therapy and/or radiation in addition to ADT in the population of interest, however the balance of effects across the individual therapies is variable.

3.2 Considerations regarding resource requirements and cost-effectiveness

The health economic analysis consists of 3 components, a health economic literature review which did not include data form Switzerland, a cost-effectiveness analysis from the Swiss healthcare payer perspective, including direct costs irrespective of payer, and a budget impact analysis for Switzerland. The methods are described in detail in the corresponding Assessment Report.

3.2.1 Evidence

3.2.1.1 Health economic literature review

Eleven eligible cost-effectiveness analyses in patients diagnosed with mHSPC were identified. Four studies were from China/Hong Kong[35-37], three from North America (USA or Canada)[38,39], two from

Brazil[40-42], one from the UK[43], and one from Spain[44]. Six studies compared the combination of ADT + docetaxel with ADT treatment alone[37,38,40,43-45], and four studies compared ADT + abiraterone with ADT + docetaxel or ADT alone[35,39,41,42]. One study, while focusing on maximum androgen blockade (through flutamide and bicalutamide + ADT), also provided a comparison of ADT + docetaxel and ADT alone[36]. No studies investigating the cost-effectiveness of ADT + enzalutamide, ADT + apalutamide, or ADT + radiotherapy were identified. For the cost-effectiveness review, three studies did not report relevant information and were subsequently excluded [40,41,44].

The range of mean costs for the treatments studied varied considerably, from USD 26,450 to USD 216,057 for docetaxel, USD 226,183 to USD 669,177 for abiraterone, and USD 10,350 to USD 205,573 for ADT alone for 3 year or life-time horizons respectively. The variability in costs between studies may reflect the different time horizons, types of direct costs included, and different unit costs. Cost differences were less variable, ranging from USD 2,057 (lifetime horizon) to USD 19,837 (15-year time horizon) between ADT + docetaxel and ADT, and from USD 199,733 (3-year time horizon) to USD 453,120 (lifetime horizon) between ADT + abiraterone and ADT + docetaxel. Similar ranges were found for ADT + abiraterone compared to ADT alone.

The range of mean absolute QALYs per treatment option were 1.53 (3-year time horizon) to 5.03 (lifetime horizon) for docetaxel, 1.73 (3-year time horizon) to 4.37 (lifetime horizon) for Abiraterone and 1.21 (3-year time horizon) to 4.02 (lifetime horizon) for ADT alone (Table 3). The differences in QALY gained for ADT + docetaxel vs. ADT were 0.20 QALYs (20-year time horizon) to 1.06 QALYs (15-year time horizon), and for ADT + abiraterone vs. ADT + docetaxel were 0.20 QALYs (3-year time horizon) to 1.54 QALYs (lifetime horizon). These figures yielded incremental cost effectiveness ratios (ICERs) of USD 4,033 (lifetime horizon) to USD to USD 50,489 (3 year horizon) for ADT + docetaxel vs. ADT, USD 295,212 (lifetime horizon) to USD 1,009,975 (3 year horizon) for ADT + abiraterone vs. ADT + docetaxel, and USD 188,085 (lifetime horizon) to USD 415,063 (3 year horizon) for ADT + abiraterone vs. ADT + docetaxel (Table 3). The major factor impacting ICERs was drug costs, with a range of monthly costs of USD 550 – 1208 for docetaxel and USD 4302 – 9399 for abiraterone. In sensitivity analyses the major factors impacting the reported CEAs were cost of treatment, transition probabilities from progression-free disease to progressive disease, survival assumptions, utilities scores.

Despite the high heterogeneity, the results of the selected cost-effectiveness suggest that ADT + docetaxel may be cost-effective compared to ADT. ADT + abiraterone either compared to ADT alone or ADT + docetaxel concluded was not cost-effective.

3.2.1.2 Cost-effectiveness analysis

The CEA was performed utilizing the data from the health economic literature review and consultation with two Swiss experts in prostate cancer, and was informed by the findings of the clinical systematic review. Drug prices, inpatient and outpatient costs were sourced from official and publicly available Swiss sources. The analysis was from the perspective of the Swiss health care payer and the Markov model considered 3 mutually exclusive health states (PF, progression, death). Estimation of survival curves was based on 6 studies (ENZAMET and LATITUDE excluded).

Over a 15 year time horizon, in the base case analysis cost-effectiveness model, ADT + docetaxel and ADT monotherapy would be associated with mean costs of CHF 70,956 and CHF 55,926, and mean

QALYs of 4.07 and 3.24, respectively (Table 3). The resulting ICER for ADT + docetaxel was CHF 18,124 per QALY gained. In contrast, ADT + abiraterone and ADT + enzalutamide resulted in high ICERs above CHF 100,000 per QALY gained (CHF 154,477/QALY for ADT + abiraterone vs. ADT**;** CHF 294,163/QALY for ADT + abiraterone vs. ADT + docetaxel; CHF 180, 872/QALY for ADT + enzalutamide vs. ADT; CHF 1,066,633/QALY for ADT + enzalutamide vs. ADT + abiraterone, Table 3). ADT + apalutamide was found to be a dominated strategy (i.e. generating higher costs and lower QALYs relative to comparators). When LATITUDE and ENZAMET were excluded in the estimation of treatment effects (HRs) and time horizon was restricted to 5 years, ADT + enzalutamide also became dominated. In further deterministic sensitivity analyses, all ICERs comparing ADT + docetaxel vs. ADT alone were below CHF 25,000 per QALY gained, whereas in comparisons of ADT + abiraterone vs. ADT + docetaxel, the ICERs were always estimated above CHF 100,000 per QALY gained.

In summary, the cost-effectiveness analysis suggests that the ICER of ADT + docetaxel vs. ADT has a point estimate of CHF 18,124 and is most likely below the putative Swiss willingness to pay threshold of CHF 100,000 per QALY gained. The novel hormonal treatments are all likely above this value at current prices in Switzerland.

3.2.1.3 Budget impact analysis

It is estimated that the total number of prostate cancer patients in Switzerland will increase from approximatively 33,300 cases in 2020 to more than 41,000 in 2030. Assuming that the age-specific frequencies of mHSPC among prostate cancer patients will remain constant, the estimated total number of newly diagnosed mHSPC cases was estimated to increase from 837 in 2020 to more than 1,000 in 2030 (+23%). The BIA was based on these estimates and considered up to 5-year follow-up costs (including drug and administration costs, AEs costs, palliative care costs, imaging costs, and end of life costs).

The BIA suggested that the total costs of treatment for mHSPC in Switzerland strongly depend on the treatment strategy. Estimated mean costs per patient per treatment strategy over 5 years were CHF 44,046 for ADT alone, CHF 56,608 for ADT + docetaxel, CHF 205,554 for ADT + abiraterone, CHF 233,930 for enzalutamide and CHD 187,205 for apalutamide. If all patients were treated with a single strategy, using 2020 costs, ADT alone (CHF 35.7 million) and ADT + docetaxel (CHF 46.3 million) would be less expensive than ADT + abiraterone (CHF 169.4 million), ADT + enzalutamide (CHF 188.7 million), or ADT + apalutamide (more than CHF 151.1 million). The total costs of treatment therefore strongly depend on the assumed relative proportional distribution of use of each therapy which is currently unknown in Switzerland. For example, assuming 50% of the eligible patients would be treated with ADT alone, 25% with ADT + docetaxel, and 25% with ADT + abiraterone would have resulted in total costs of CHF 70.9 million in 2020, CHF 35.2 million more than treatment with ADT alone. In practice expert opinion suggests that the use of the investigated novel hormonal treatments among mHSPC patients is in constant evolution and may change very fast in the next few years.

In summary, the BIA suggests that treatment strategies mainly based on ADT alone or ADT + docetaxel led to the lowest total costs. Alternative assumptions considering the use of novel hormonal treatments led to significantly higher total costs.

3.2.1.4 Additional considerations

In the CEA, the most substantial cost components for all novel hormonal mHSPC treatments were the costs of the drugs themselves. Specifically, drug acquisition and drug administration costs in total represented 91% of the overall costs for ADT + enzalutamide, 89% for ADT + abiraterone, 88% for ADT + apalutamide, 58% for ADT + docetaxel costs, and 39% for ADT. Using a hypothetical price of abiraterone of CHF 1,250 (the current public price is CHF 3,529.05) yielded an estimated an ICER of CHF 97,442/QALY gained for ADT + abiraterone in relation to ADT + docetaxel. At this price, the ICER for ADT + abiraterone vs. ADT monotherapy reduces to CHF 56,012. Note that the price of abiraterone has come under pressure recently as cheaper generic substitutes have become available.

The BIA presumed immediate treatment upon diagnosis of mHSPC and did not consider a delay in costs which may occur with a "watch and wait" strategy (Figure 1). The 5-year cost of ADT + docetaxel per patient compared with ADT alone would be CHF 12,000, representing an increase of 25%. This amount is not relevant given that ADT + docetaxel has an an ICER equal of CHF18'000.

3.2.1.5 Judgment

The Appraisal Committee concluded that from the perspective of the Swiss healthcare payer the cost-effectiveness of the systemic therapies in addition to ADT varies, as ADT + docetaxel is cost-effective in the population of interest, and this strategy dominates the novel hormonal therapies at current prices. No judgment could be reached on the cost-effectiveness of radiation. The budget impact for the Swiss healthcare payer of the additional use of docetaxel is small, whereas that associated with the additional use of the novel hormonal therapies is large.

3.2.2 Certainty of evidence with regard to resource requirements

Health economic literature review

An important strength of the health economic literature review was that most data was based on RCTs included in the clinical systematic review and was therefore relevant to the analysis, however no studies were identified evaluating cost-effectiveness of ADT + enzalutamide, ADT + apalutamide, or ADT + radiotherapy vs. ADT alone. Data from Switzerland was not available, although studies from USA, Canada and the UK could be considered broadly similar from a socioeconomic perspective. According to the CHEERS checklist, the quality of reporting differed substantially between the eleven eligible studies. Since three studies did not report important information (e.g. details of study population, perspective, comparator, time horizon, or results in terms of incremental costs and outcomes), only the results of eight out of 11 cost-effectiveness studies were considered.

The adopted perspectives, time horizons, and types of costs and discount rates considered were variable across studies. Due to the heterogeneity in the reported input parameters and underlying

sources it was not possible to directly compare the effectiveness assumptions across the different cost-effectiveness analyses. As an indicator of inter-study variability, among those adopting a lifetime horizon, the QALY differences between ADT + docetaxel vs. ADT alone were 0.30 QALYs, 0.51 QALYs, 0.79 QALYs and 1.01 QALYs in 4 different studies.

Cost Effectiveness Analysis.

Strengths of the three-health state Markov models were that the model parameters were obtained from the prior full clinical and health economic literature searches. The pooled ADT survival curve was calculated with sound information. The OS and PFS HRs from a literature-based NMA were used in one set of analyses, and individual patient OS and PFS were re-created and analyzed in another set of analyses. ICER results generated using OS and PFS HRs derived from either dataset were consistent. Drug, inpatient and outpatient costs were all sourced from official Swiss sources and two Swiss medical experts were consulted to verify or obtain resource use values and assumptions that were appropriate for Switzerland.

Limitations of the CEA included weakness of input data resulting from lack of Swiss-specific estimates, lack of sufficient data types of AE, and the reliance on multiple assumptions about utilities, treatment courses, frequencies of use of additional medication, palliative care costs, costs of routine follow up, and compliance rates, as well as extrapolation of OS and PFS estimates to 15 years of follow-up, and exclusion of radiation from in the analysis. In addition, analyses used lowest identified prices in calculations. Probabilistic sensitivity analyses revealed wider scattering of points across the x-axis than across the y-axis suggesting considerable uncertainty in the ICER in relation to the magnitude of the QALYs estimated for each treatment strategy. As in the clinical NMA, enzalutamide data should be treated with caution, until longer-term data is available. Costs associated with subsequent treatment strategies for castration resistant prostate cancer could not be considered. Only the healthcare payer perspective was considered.

Budget Impact Analysis

Strengths of the BIA included the use of the undiscounted costs, which included drug and administration costs, AEs costs, palliative care costs, imaging costs, and end of life costs happening during the first 5 years of treatment.

Specific concerns regarding the BIA include the potential of overcounting by combining incident and prevalent patients, extrapolations of eligibility for treatment based on international data for percentages of mHSPC and assumption of stable proportions over time. In addition, there is a lack of information on the current Swiss standard of care and the distribution of use of the investigated treatments for mHSPC, which may vary considerably across hospitals and regions, patient characteristics, cancer volume and treating physicians. Only short-term costs of mHSPC treatment were included (i.e. over 5 years) and costs extrapolations assumed constant treatment distributions until 2030. Potential changes in drug prices over time were not considered.

3.2.2.1 Judgment

The Appraisal Committee concluded that the certainty of evidence regarding resources required for the addition of systemic therapies to ADT in the population of interest is high.

3.3 Health equity

A search of published evidence of health equity in relation to use of additional therapies for mHSPC was not part of the assessment. The HTA did not consider social, legal, organizational impacts or implications of these therapies. Input from two Swiss experts suggested unknown variability in utilization of the novel additional therapies in Switzerland. Decision-making regarding treatment choices is likely being made on an individual basis given the lack of clear data suggesting superiority of one strategy over another, but some variability on HRQoL. It is possible that access to the novel hormonal therapies, being expensive, may be somewhat dependent on health insurer and patient insurance status (private, half-private or general insurance), as well as conviction of the treating clinician. Variability in access to care is currently unknown.

3.3.1 Judgment

The Appraisal Committee concluded that there is probably no impact on health equity of systemic therapies and/or radiation in addition to ADT in the population of interest.

3.4 Acceptability

From the systematic review there is no data on patient acceptability of the individual novel additional therapies for mHSPC. All systemic treatments improved OS and the MID thresholds were not met for most HRQoL scores. It is likely that individual tolerance for potential AEs is variable. All therapies are currently in use. The Swiss experts did not favour one treatment over another.

3.4.1 Judgment

The Appraisal Committee concluded that the use of systemic therapies and/or radiation in addition to ADT in the population of interest are acceptable to key stakeholders. This judgment excludes any consideration of effectiveness or safety of the intervention.

3.5 Feasibility

All therapies currently in use, their implementation is therefore likely feasible. The sustainability of use of the more expensive novel hormonal therapies over the longer term is unknown. The potential for combinations of sequential use of the various therapies in improving outcomes is not known.

3.5.1 Judgment

The Appraisal Committee concluded that use of systemic therapies and/or radiation in addition to ADT in the population of interest is feasible.

4 Recommendations

The Appraisal Committee issued a conditional recommendation in favor of the use of systemic therapies and/or radiation in addition to ADT men with newly diagnosed mHSPC who had not undergone prior systemic therapy.

Justification

The assessment of the clinical effectiveness showed that ADT + docetaxel, ADT + abiraterone, ADT + enzalutamide and ADT + apalutamide are all effective in improving survival in patients with newly diagnosed mHSPC. ADT + radiotherapy only conferred a survival benefit among patients with low-volume de novo mHSPC. Although there was no statistically significant overall benefit of one of the additional systemic mHSPC treatments over another, the novel hormonal treatments tended to show a greater survival benefit, and had a statistically significantly greater effect on PFS compared to ADT + docetaxel. Longer-term HRQoL was improved with ADT + abiraterone compared to ADT alone, while ADT + docetaxel appeared to lead to a short-term HRQoL decline but better preservation of HRQoL over the longer term compared with ADT alone. No consistent effect on overall HRQoL was found for ADT + enzalutamide and ADT + apalutamide compared to ADT alone. Novel hormonal treatments may provide a greater net clinical benefit for patients due to higher rates of severe adverse events with ADT + docetaxel. In contrast, when relating the costs to the clinical benefit, the cost-effectiveness analysis with a 15-year time horizon showed that ADT + docetaxel was the only cost-effective treatment option from a Swiss healthcare payer perspective based on current drug prices. In general, novel hormonal therapies are associated with increased costs for the healthcare system, the current magnitude of which is unknown. Costs of radiation were not examined.

Subgroup considerations

Overall, robust stratification by clinical subgroups was limited and outcome analyses could be impacted by small numbers and limited accrual times. Subgroup analysis for HRQoL was provided in only one RCT and no judgement was possible on AEs across subgroups.

In subgroup analyses, a statistically significant survival benefit was observed for all novel hormonal treatments, but not for ADT + docetaxel in the low-volume subgroup. All systemic combination treatments conferred a statistically significant survival benefit over ADT alone in the high-volume and the *de novo* diagnosed mHSPC subgroups. ADT + Apalutamide was the only therapy with a significant effect in the subgroup who had undergone prior local therapy. All systemic therapies conferred a benefit in both performance status subgroups. Data for enzalutamide was not considered in most subgroup analyses. ADT + radiotherapy provided a statistically significant benefit in low-volume, but not in high-volume *de novo* mHSPC. In terms of HRQoL, FACT-P scores declined significantly in men with low volume disease receiving ACT + Docetaxel at 3 months compared with ADT alone, but more pronounced deterioration in HRQoL was observed over time in men treated with ADT alone at all time points in the low volume subgroup, and at 12 months in men in the high-volume subgroup.

Implementation considerations

Effective and transparent communication with patients is necessary to enable shared decision making. Patients' perception of treatment options and their preferences and values should be considered before a decision is made. Given the lack of clear superiority of one strategy over another, except for limited benefit of some superiority in some subgroups, patient preferences and coverage by the health insurer will impact choice of treatment strategy. All treatments are in current use and therefore appear feasible and acceptable.

Monitoring and evaluation

All treatments included in this HTA are currently being implemented. The distribution of their use in Switzerland is currently not known and the cost-effectiveness is also unknown. It is imperative that the value of the various interventions is better understood given the clear differences in costs as well as the potential differences in impact on HRQoL and AEs, and specifically within various patient subgroups where benefits or risk of potential harms may be greater and access may differ by region, payer or prescriber.

Research priorities

Long-term studies investigating clinical benefit, cost-effectiveness, and acceptability of the systemic therapies and radiation in adult men with newly diagnosed mHSPC who have not undergone prior systemic therapy. Specifically, data is required in patient preferences and values regarding the balance between potential benefits and the impact on HRQoL or AEs. More data is required within subgroups to define whether one therapy may indeed be superior to another in terms of benefit or harm. The value and impact of transitions from one therapeutic strategy to another also require study. Longitudinal studies are required to capture disease trajectories, potential switches of therapeutic strategies, changes in HRQoL or risk of AEs over time as well as to track patient preferences and costs over time. Support for national disease registries would facilitate such data collection and analysis, as well as pharmacovigilance to accurately track incidence, severity and duration of AEs. The Appraisal Committee recommends a collaborative research effort across Switzerland to fill such knowledge gaps. Prospective cost-effectiveness studies should provide more reliable data for future health economic assessments from the societal perspective.

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Table 1: Summary of effects on survival

	Overall Survival (OS)							Progression free survival (PFS)*	
		Subgroups							
	Overall HR (95% CI)	**Low volume HR (95% CI)**	**High volume HR (95% CI)**	**De novo HR (95% CI)**	**Prior local Therapy HR (95% CI)**	**ECOG 0 HR (95% CI)**	**ECOG ≥1 HR (95% CI)**	**Overall HR (95% CI)**	**Low volume HR (95% CI)**
Docetaxel + ADT vs. ADT	**0.77 (0.69- 0.85)**	0.91 (0.73 – 1.13)	**0.72 (0.63 – 0.84)**	**0.79 (0.70 – 0.89)**	0.90 (0.62 – 1.32)	**0.82 (0.71 – 0.93)**	**0.70 (0.56 – 0.87)**	**0.67 (0.60 – 0.74)**	-
Abiraterone + ADT vs. ADT	**0.66 (0.58 – 0.74)**	**0.67 (0.50 – 0.91)**	**0.62 (0.53 – 0.71)**	**0.64 (0.56 – 0.73)**	0.94 (0.35 – 2.52)	**0.67 (0.56 – 0.80)**	**0.57 (0.46 – 0.71)**	**0.46 (0.41 – 0.52)**	-
Enzalutamide + ADT vs. ADT	**0.63 (0.48 – 0.83)**	**0.38 (0.21 – 0.69)**	**0.65 (0.42 – 1.00)**	excl.	excl.	excl	excl	**0.36 (0.30 – 0.44)**	-
Apalutamide + ADT vs ADT	**0.65 (0.53 – 0.79)**	**0.52 (0.35 – 0.78)**	**0.70 (0.56 – 0.88)**	**0.68 (0.55 – 0.85)**	**0.39 (0.22 – 0.69)**	**0.68 (0.52 – 0.89)**	**0.56 (0.42 – 0.75)**	**0.49 (0.39 – 0.62)**	-
Abiraterone + ADT vs. Docetaxel + ADT	0.86 (0.73 -1.01)	-	-	-	-	-	-	**0.69 (0.59 – 0.8)**	-
Enzalutamide + ADT vs. Docetaxel + ADT	0.82 (0.61 – 1.10)	-	-	-	-	-	-	**0.58 (0.44 – 0.77)**	-
Apalutamide + ADT vs. Docetaxel + ADT	0.8 (0.68 – 1.06)	-	-	-	-	-	-	**0.73 (0.57 – 0.95)**	-
Enzalutamide + ADT vs. Abiraterone + ADT	0.96 (0.71 – 1.30)	-	-	-	-	-	-	NS	-
Apalutamide + ADT vs. Abiraterone + ADT	0.99 (0.78 – 1.26)	-	-	-	-	-	-	NS	-
Apalutamide + ADT vs. Enzalutamide + ADT	1.03 (0.74 – 1.45	-	-	-	-	-	-	NS	-
Radiation + ADT vs. ADT	0.91 (0.81 – 1.03)	**0.68 (0.54 – 0.86)**	1.07 (0.92 – 1.24)	0.91 (0.92 – 1.03)	-	0.91 (0.79 – 1.05)	0.97 (0.77 – 1.22)	0.96 (0.85 – 1.08) **0.76** (0.69 – 0.84)**	**0.78 (0.63 – 0.97)**

*PFS includes clinical, radiographic and biochemical;** result for biochemical PFS only**;** excl. – excluded; NS - non-significant; **Bold** = p value significant

Table 2. Results and GRADE assessment for the direct and indirect evidence from the included studies on the effects of systemic mHSPC treatments and radiotherapy on overall survival

Comparison	Direct Estimate* HR (95%CI)	Direct Estimate* Rating	Indirect Estimate** HR (95%CI)	Indirect Estimate** Rating	NMA Estimate HR (95%CI)	NMA Estimate Rating
Docetaxel + ADT vs. ADT	**0.79 (0.71 to 0.89)**	High	**0.56 (0.38 to 0.81)**	Low	**0.77 (0.69 to 0.85)**	High
Abiraterone + ADT vs. ADT	**0.64 (0.56 to 0.73)**	Moderate	**0.89 (0.60 to 1.34)**	Very low[d]	**0.66 (0.58 to 0.74)**	Moderate[e]
Enzalutamide + ADT vs. ADT	**0.63 (0.48 to 0.83)**	Low[b, c]	-	-	**0.63 (0.48 to 0.83)**	Low
Apalutamide + ADT vs. ADT	**0.65 (0.53 to 0.79)**	High	-	-	**0.65 (0.53 to 0.79)**	High
Abiraterone + ADT vs. Docetaxel + ADT	1.13 (0.77 to 1.66)	Low[a, d]	**0.81 (0.68 to 0.96**)	High	0.86 (0.73 to 1.01)	Moderate[e]
Enzalutamide + ADT vs. Docetaxel + ADT	-	-	0.82 (0.61 to 1.10)	Very low[d]	0.82 (0.61 to 1.10)	Very low[d]
Apalutamide + ADT vs. Docetaxel + ADT	-	-	0.85 (0.68 to 1.06)	Moderate[d]	0.85 (0.68 to 1.06)	Moderate[d]
Enzalutamide + ADT vs. Abiraterone + ADT	-	-	0.96 (0.71 to 1.30)	Very low[d]	0.96 (0.71 to 1.30)	Very low[d]
Apalutamide + ADT vs. Abiraterone + ADT	-	-	0.99 (0.78 to 1.26)	Moderate[d]	0.99 (0.78 to 1.26)	Moderate[d]
Apalutamide + ADT vs. Enzalutamide + ADT	-	-	1.03 (0.74 to 1.45)	Very low[d]	1.03 (0.74 to 1.45)	Very low[d]
Radiotherapy + ADT vs. ADT	0.91 (0.81 to 1.03)	Moderate[d]	-	-	-	-

*direct estimate – effects compared within same study; **indirect estimate – comparisons of effects not compared within the same study. Downgrading due to: [a] = Limitations in study design or execution, [b] = Inconsistency, [c] = Indirectness, [d] = Imprecision, e = Incoherence. Legend: ADT = androgen deprivation therapy, HR = hazard ratio, CI = confidence interval, NMA = network meta-analysis. (Adapted from Tables 2 and 4 in the Assessment Report)

Table 3. Summary of cost effectiveness data

	Health Economic Literature review								Cost effectiveness analysis			
	Mean absolute QALYs		**Differences in QALYs gained vs. comparator**				**ICER (USD)**		**Costs (CHF)**	**QALYs discounted**	**Pairwise ICER (CHF) relative to previous non-dominated strategy**	**Pairwise ICER vs. ADT (CHF)**
Time Horizon	3 year	Lifetime	3 year	15 year	20 year	Lifetime	3 year	Lifetime	15 years			
Docetaxel	1.53	5.03	-	-	-	-	-	-	-	-	-	-
Abiraterone	1.73	4.37	-	-	-	-	-	-	-	-	-	-
ADT	1.21	4.02	-	-	-	-	-	-	55,926	3.24	-	-
Docetaxel + ADT vs. ADT	-	-	-	1.06	0.2	-	50,489	4,033	70,956	4.07	18,124	18,124
Abiraterone + ADT vs. ADT (current price of CHF 3529.05)	-	-	-	-	-	-	415,063	188,085	309,089	4.88	-	154,477
*Abiraterone + ADT vs. ADT (hypothetical price of CHF 1250.00)**									*147,785*	*4.88*		*56,012*
Abiraterone + ADT vs. Docetaxel + ADT (current price of CHF 3529.05)	-	-	0.2	-	-	1.54	1,009,975	295,212	309,089	4.88	294,163	-
*Abiraterone + ADT vs. Docetaxel + ADT (hypothetical price of CHF 1250.00)**									*147,785*	*4.88*	*97,442*	
Enzalutamide + ADT vs. ADT	-	-	-	-	-	-	-	-	361,179	4.93	-	180,872
Enzalutamide + ADT vs. Abiraterone + ADT	-	-	-	-	-	-	-	-	-	-	1,066,633	-
Apalutamide + ADT	-	-	-	-	-	-	-	-	295,750	4.59	dominated	dominated

*the price for Abiraterone is coming under increased pressure with release of generics making price reductions in the near future a possibility

Figure 1: Treatment options for newly diagnosed and hormone-sensitive prostate cancer

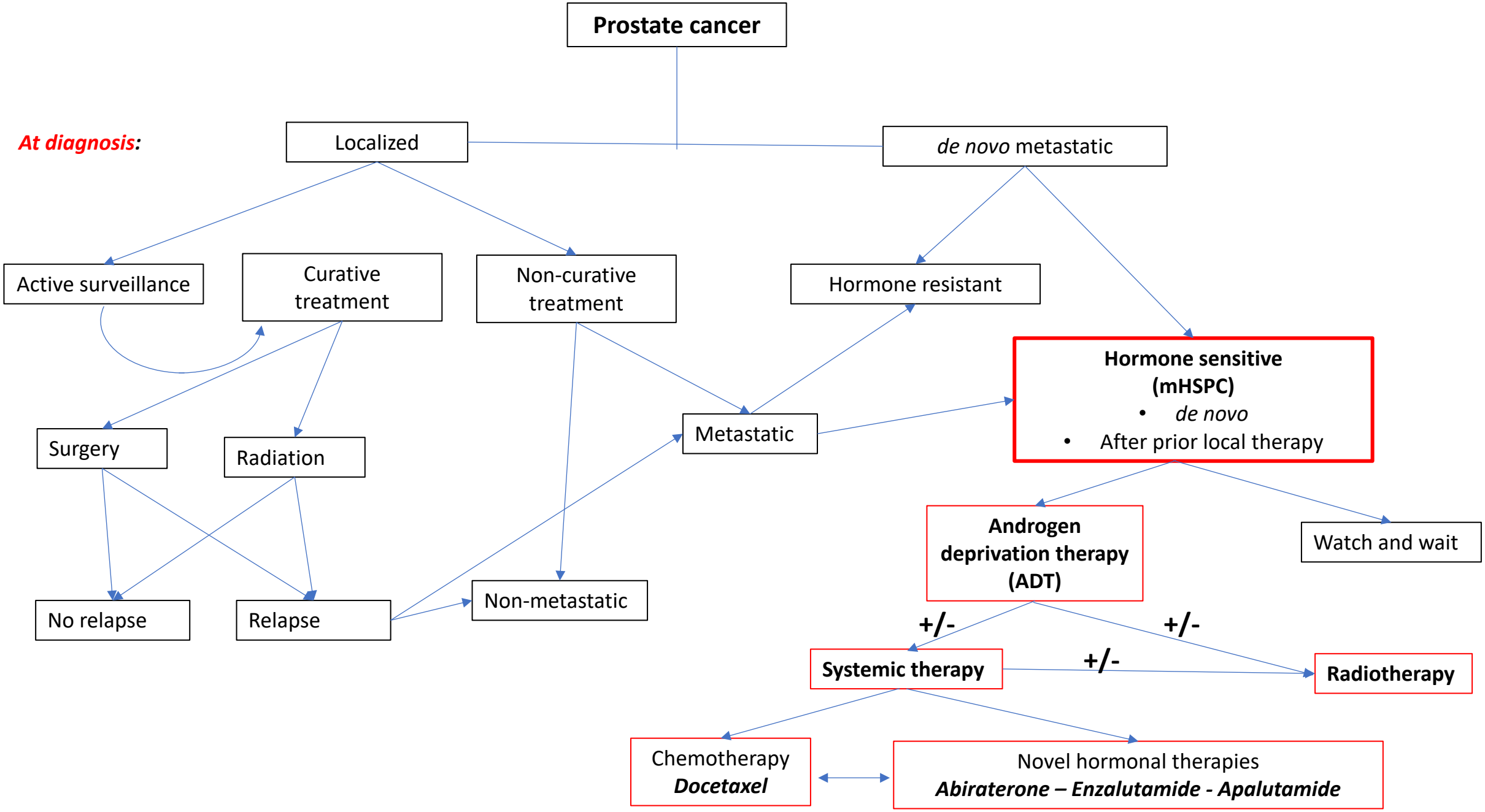
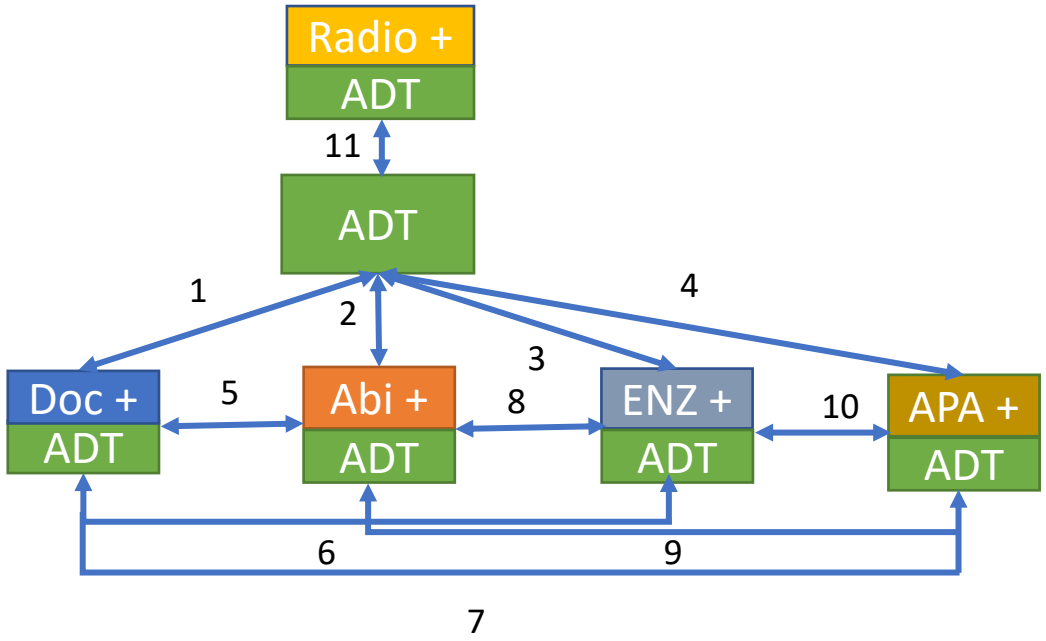


Figure 2: Treatment options and comparators evaluated in the Assessment Report



Comparison	Label	Studies
Docetaxel + ADT vs. ADT	1	GETUG-AFU 15; CHAARTED, STAMPEDE
Abiraterone + ADT vs. ADT	2	STAMPEDE, LATITUDE
Enzalutamide + ADT vs. ADT	3	ENZAMET, ARCHES
Apalutamide + ADT vs. ADT	4	TITAN
Abiraterone + ADT vs. Docetaxel + ADT	5	STAMPEDE
Enzalutamide + ADT vs. Docetaxel + ADT	6	-
Apalutamide + ADT vs. Docetaxel + ADT	7	-
Enzalutamide + ADT vs. Abiraterone + ADT	8	-
Apalutamide + ADT vs. Abiraterone + ADT	9	-
Apalutamide + ADT vs. Enzalutamide + ADT	10	-
Radiotherapy + ADT vs. ADT	11	STAMPEDE, HORRAD