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

Health Technology Assessment Report

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Abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse Effect
CBA	Cost-Benefit Analysis
BFI	Brief Fatigue Inventory
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
nsAA	Non-Steroidal Anti-Androgens
OS	Overall Survival
PD	Progressive Disease
PFS	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
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

Executive Summary

Introduction

Prostate cancer is the most frequent cancer in men, placing a high burden on patients and healthcare systems. Prostate cancer is characterised by a relatively slow disease progression and typically responds well to treatments that reduce the production of androgens (e.g. testosterone). In metastatic hormone-sensitive prostate cancer (mHSPC), such androgen deprivation therapy (ADT) has long been considered the standard of care. Patients with mHSPC have either never undergone ADT before or show ongoing sensitivity to ADT. mHSPC is typically diagnosed either at first diagnosis of prostate cancer (i.e., *de novo*), or as a progression after local treatment of the primary tumour (i.e., progression after prior local therapy). Several different treatments have now become available that have been shown to substantially improve the prognosis of patients with mHSPC when given in combination with ADT.

Treatment options in mHSPC currently involve ADT alone, or in combination with chemotherapy (docetaxel), novel hormonal therapies (abiraterone, enzalutamide or apalutamide), or radiotherapy. The available treatments differ in terms of their effects on survival, disease progression, health-related quality of life, and adverse effects, as well as their costs. The optimal treatment for men with mHSPC both diagnosed *de novo* or progressing after prior local therapy is thus currently debated. This Health Technology Assessment (HTA) aims to evaluate the clinical effectiveness, safety, benefit-harm balance and health economic characteristics of docetaxel, abiraterone, enzalutamide, apalutamide and radiotherapy in combination with ADT among each other and compared to ADT alone in patients with mHSPC, in Switzerland.

Methods

PICO
The **population of interest** for this HTA were adult men with newly diagnosed mHSPC– both diagnosed *de novo* and progressing after prior local therapy – that had not previously undergone systemic therapy.

We investigated the following **interventions**:

- ADT + docetaxel (75mg/m^2 body surface area, administered i.v. every 3 weeks for 6 cycles) + prednisone 10mg/day for 6 cycles
- ADT + abiraterone acetate (1,000mg/day p.o.) + prednisone 5mg/day
- ADT + enzalutamide (160mg/day p.o.)
- ADT + apalutamide (240mg/day p.o.)

In the assessment of the clinical efficacy and safety, we additionally evaluated ADT + radiotherapy (external beam radiation therapy to the prostate, followed by ADT alone) as a complementary intervention to the aforementioned systemic mHSPC treatments.

We considered the following **comparator** treatments:

- ADT alone or in combination with placebo (licensed dose). ADT may involve orchidectomy or treatment with gonadotropin-releasing hormone agonists or antagonists.
- ADT + first-generation non-steroidal antiandrogens (nsAA)

We defined the following **outcomes** of interest:

- Overall survival (OS)
- Health-related quality of life (HRQoL)
    - Overall HRQoL measured by EQ-5D, SF-36, EORTC QLQ-C30
    - Prostate cancer-specific quality of life measured by: FACT-P, FACIT-F, Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI).
- Progression-free survival (PFS)
    - Primarily clinical (cPFS) or radiographic PFS (rPFS), alternatively failure-free survival (FFS) or biochemical PFS (bPFS).
- Adverse effects (AEs)
- Costs, quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs) with QALYs in the denominator

We determined the following **subgroups** of interest for the assessment of the clinical efficacy and safety:

- High- vs. low-volume disease (according to CHAARTED; high volume disease is defined as either of the following two criteria: visceral metastases or ≥4 bone lesions with ≥1 outside of the vertebral bodies and pelvis)
- *De novo* mHPSC vs. progression after prior local therapy
- Restricted physical performance vs. unrestricted performance (Eastern Cooperative Oncology Group (ECOG) Performance Status ≥1 vs. 0).

Assessment of Clinical Efficacy and Safety

We conducted a systematic literature review and network meta-analysis (NMA) to determine the effects of the different mHSPC treatments compared to ADT alone as well as relative to each other. We searched MEDLINE, EMBASE, CENTRAL and ClinicalTrials.gov until February 2020 and screened relevant conference proceedings since 2016 up to April 2020 for relevant records of randomised controlled trials (RCTs). We performed a full standardised screening and assessment process for all identified records and extracted data from eligible RCTs in duplicate. We assessed the identified RCTs regarding their risk of bias on an outcome-basis using the RoB 2.0 tool.

We conducted frequentist random-effects NMAs based on aggregate-level data reported by the RCTs. We evaluated the appropriateness of combining the evidence from different RCTs in meta-analysis and conducted sensitivity analyses where deemed appropriate (relevant for RCTs LATITUDE, ENZAMET, and STAMPEDE). We analysed effects for ADT + radiotherapy separately, as this treatment choice is independent of the choice of systemic treatment and is only indicated in *de novo* mHSPC. For AEs, we calculated trial-level incidence rates based

on events and person-time at risk (using median follow-up time). We then calculated trial-level incidence rate ratios, which we combined into treatment-level estimates using meta-analysis. We further narratively synthesised results where meta-analysis was not possible. Last, we assessed the quality of the available evidence for the critical effectiveness outcomes according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for network meta-analyses.

Benefit-Harm Assessment

This assessment considered the benefit and harm outcomes of ADT + docetaxel, ADT + abiraterone, ADT + enzalutamide, and ADT + apalutamide in order to determine the benefit-harm balance or a net clinical benefit from a clinical decision-making perspective. We used an approach developed by Gail et al. to simultaneously take into account relative treatment effects, outcome risks without taking the intervention treatments, and importance of outcomes (patient preferences) to assess the benefit-harm balance of the different systemic mHSPC treatments.

We used the risk reduction in all-cause death (i.e., deaths averted due to treatment) as the benefit outcome, and grade 1-2 AEs and grade 3-4 AEs (according to the Common Terminology Criteria for Adverse Events (CTCAE)) as the harm outcomes in the model. We used the following parameter inputs for our analysis:

- Relative treatment effects: incidence rate ratios were calculated to estimate the risk reduction of all-cause death as well as excess risk of harms (i.e., grade 1-2 AEs and grade 3-4 AEs), based on data collected within the systematic review and network meta-analysis (see assessment of clinical efficacy and safety).
- Outcome risks: we used average all-cause death rates, as well as grade 1-2 AEs and grade 3-4 AEs calculated from patients treated with ADT alone in the included RCTs (all-cause death rate: 8.9 per 1,000 patient-months, 95% CI 7.1 to 11.1; grade 1-2 AEs: 21.6 per 1,000 patient-months, 95% CI 13.5 to 34.5; and grade 3-4 AEs: 10.4 per 1,000 patient-months, 95% CI 5.8 to 18.8).
- Preferences weights: preference weights represent the relative importance (or severity) of outcomes, where a higher value means that patients have a greater preference for avoiding the outcome. Due to the lack of empirical evidence on patient preferences from patient preference studies in mHSPC, we used generic values for all-cause death (1.00 on a 0 to 1 scale), grade 1-2 AEs (0.18) and grade 3-4 AEs (0.53). These weights were based on values previously used in BHAs in other decision contexts including breast cancer, which were then evaluated for transferability based on severity and consequences for patients and a comparison to the limited available evidence from preference studies.
- Time horizon: the cumulative net clinical benefit of the mHPSC treatments was assessed over a 24-month time horizon. 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.

Assuming constant rates of all-cause death and AEs over 24 months, the cumulative risks of these outcomes were estimated using an exponential model for a theoretical cohort of 1,000

patients receiving the mHPSC treatment interventions. The expected cumulative risks of the outcomes were again estimated for the same size cohort treated with ADT alone. The absolute differences in incidence rates of the outcomes with and without the interventions were then calculated and subsequently weighted individually based on the patient preferences for those outcomes. The estimates for each benefit and harm outcome were added up to a benefit-harm balance index or net clinical benefit. The index shows whether the benefits outweighed the harms (positive index) or vice versa (negative index), or whether neither benefits nor harms outweighed the other (index equals zero). The analysis was performed stochastically with 100,000 repetitions accounting for the uncertainty of parameter estimates to generate a distribution of the benefit-harm balance index. From the distribution of the index, we calculated the probability that patients receiving the interventions would experience a clinical net benefit. Probability above 60% was interpreted as net clinical benefit (or more clinical benefit than harms), below 40% were interpreted as net harm (less benefits than harms) or as neither harmful nor beneficial (40 to 60%). In addition, we estimated the absolute expected events for all-cause death and grade 1-2 AEs and grade 3-4 AEs over the 24-month time horizon. Since BHA is highly dependent on the selection of evidence for the input parameters, we tested the sensitivity of the net clinical benefit to different alternative estimates. This included the use of a longer time horizon (60 months), lower preference weights (0.05 for grade 1-2 AEs and 0.25 for grade 3-4 AEs), a higher all-cause death rate (17.9 per 1,000 patient-months; aggregated estimate based on pooled reconstructed RCT data from health economic assessment), alternative measures for relative treatment effect based on network meta-analysis, as well as the exclusion of RCTs with uncertainties regarding the reported data (e.g., LATITUDE, ENZAMET).

Health Economic Literature Review

For the economic systematic review, search strategy was developed to identify all relevant literature in in MEDLINE, EMBASE, and the Cochrane library. The search string was obtained by integrating and combining the search string used in the clinical part of this assessment report, and published search strings for health economic analyses. A two-phase process consisting of title/abstract and full text screening was conducted. Data extraction and quality assessment according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 24-item checklist was conducted for all articles reporting a full-scale health economic evaluation study. Population demographics and study characteristics were summarised. Measurement and sources of clinical effectiveness and costs were synthesised, and results of the cost-effectiveness analyses covering different treatments comparisons within one study as well as across studies were described.

Cost-Effectiveness Analysis

We 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. To do so, we developed a 3-state Markov cohort simulation model with mutually exclusive health states of progression-free disease, progressive disease (PD) and death. Due to the poor prognosis of mHSPC patients and based on an extrapolation of pooled survival data from RCTs included in this assessment, a 15-year time horizon was selected. The model applied a discount rate of 3% for costs and effects, and a cycle length of 1 month. We assumed that after progression to the castration resistant prostate cancer (CRPC) state of the disease,

patients would receive palliative care, or either one or two further lines of treatment, the latter again followed by palliative care.

In order to obtain the transition probabilities for the health economic model, we performed a meta-analysis (Cox frailty model) of re-created OS and PFS curves for ADT treatment sourced from several RCTs. For this, we digitalised the published OS and PFS curves and re-created individual patient data (IPD). We extrapolated the pooled OS and PFS curves under ADT to the 15-year time horizon with the best-fitting parametric distribution. For the intervention strategies, we obtained OS and PFS curves by combining the pooled ADT curves with the respective treatment effect, expressed as hazard ratios (HRs). We used HRs from the NMA of the clinical part based on aggregate-level data but also from a (Cox mixed effects) global model based on IPD data and incorporating all treatment strategies.

Drug, inpatient and outpatient costs were drawn from official and publicly available Swiss sources. We used published health state utility values, and based AE rates on the related meta-analysis performed in the clinical part. We consulted with two Swiss medical experts in order to verify or obtain resource use values and assumptions that were appropriate for Switzerland. In order to investigate parameter and structural uncertainty, we performed deterministic and probabilistic sensitivity analyses, as well as several scenario analyses.

Budget Impact Analysis
The budget impact analysis consisted of two main steps. First, the total number of eligible patients per year in Switzerland was estimated, considering patients newly diagnosed (i.e., incident cases directly staged as mHSPC) and already known prostate cancer patients that progressed after prior local therapy (i.e., prevalent cases). For this purpose, national data on prostate cancer incidence and prevalence was combined with internationally published information. All estimations were adjusted for the reported and estimated age-distribution of men in Switzerland. Second, the estimated number of eligible patients was combined with undiscounted cost results for the first five years after diagnosis from the cost-effectiveness analysis. Costs at the national level were estimated from the Swiss healthcare payer perspective until 2030.

Since the available information on the treatment distribution among mHSPC patients was inconclusive, and since the market access of the investigated treatments happened in different years, we used a standard of care treatment assumption that may represent the clinical practice before the marketing approval of abiraterone, enzalutamide, and apalutamide: 50% of the patients would receive ADT alone, whereas 50% would receive ADT + docetaxel. Several alternative assumptions, including monotherapies (e.g. all patients receive ADT + abiraterone) and combinations (e.g. 50% ADT alone, 25% ADT + docetaxel, 25% ADT + abiraterone), were analysed. For all analyses, fixed market shares were assumed, meaning that the same proportional treatment use was assumed over the entire time horizon of the analysis. In addition, we assumed that patients would not switch between different treatment strategies.

Results & Discussion

Assessment of Clinical Efficacy and Safety

We screened 2724 unique records and identified eight eligible trials for inclusion of our systematic review and network meta-analysis. We identified three RCTs investigating ADT + docetaxel (GETUG-AFU 15, CHAARTED, STAMPEDE arm C), two investigating ADT + abiraterone (LATITUDE, STAMPEDE arm G), ADT + enzalutamide (ENZAMET, ARCHES) and ADT + radiotherapy (STAMPEDE arm H, HORRAD), and one for ADT + apalutamide (TITAN), with median follow-up times ranging from 14.4 to 83.9 months. LATITUDE included only high-risk patients, ENZAMET allowed the concurrent use of docetaxel and used a combination of ADT + nsAA as the comparator intervention, and STAMPEDE also included high-risk non-metastatic patients (data for metastatic patients only often available).

In NMA, all systemic mHSPC treatments showed a statistically significant survival advantage compared with ADT alone. Analyses resulted in a hazard ratio (HR) of 0.77 (95% confidence interval (CI) 0.69 to 0.85; p<0.001) for ADT + docetaxel, a HR of 0.66 (95% CI 0.58 to 0.74; p<0.001) for ADT + abiraterone, a HR of 0.63 (95% CI 0.48 to 0.83; p<0.001) for ADT + enzalutamide, and a HR of 0.65 (95% CI 0.53 to 0.79; p<0.001) for ADT + apalutamide, each compared to ADT alone. None of the comparisons between the different interventions showed a statistically significant survival advantage of one systemic mHSPC treatment over another. In sensitivity analyses, there was considerable uncertainty regarding the evidence from ENZAMET due to the aforementioned issues and relevant differences in effects on survival compared to the ARCHES trial, which also led to relevant changes in the treatment ranking. For ADT + radiotherapy, we found no statistically significant benefit on survival in the overall mHSPC population (HR 0.91; 95% CI 0.92 to 1.03; p=0.15). We judged the quality of the evidence as high for ADT + docetaxel and ADT + apalutamide, moderate for ADT + abiraterone and ADT + radiotherapy, and low for ADT + enzalutamide.

In subgroup analyses, we found a statistically significant survival benefit for all novel hormonal treatments but no statistically significant effect for ADT + docetaxel in the low-volume subgroup, while all systemic combination treatments showed a statistically significant survival benefit over ADT alone in the high-volume subgroup. 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 one of the novel hormonal therapies in the low-volume setting. For ADT + radiotherapy, we observed a statistically significant effect in the low-volume setting, but not in high-volume *de novo* mHSPC. This is in accordance with current practice guidelines, which recommend the use of radiotherapy in combination with ADT only in low-volume *de novo* mHSPC.

Data on HRQoL-related outcomes was reported much more infrequently and substantially less consistently by the included RCTs, and we judged the risk of bias as moderate to high in five out of eight studies. For ADT + docetaxel, studies relatively consistently reported lower HRQoL and higher fatigue scores over the first 3-6 months of treatment associated with the acute effects of chemotherapy, but showed higher HRQoL beyond one year of treatment compared to ADT alone. For ADT + abiraterone, the LATITUDE trial showed marked, statistically significant benefits in HRQoL, fatigue and pain up to 2.5 years compared to ADT

alone. Data from STAMPEDE further showed a benefit of ADT + abiraterone over ADT + docetaxel for the first 6 months, but not at later time points. For ADT + enzalutamide, the ENZAMET trial showed a benefit over ADT + nsAA for fatigue, cognitive functioning and physical functioning, but not in overall HRQoL scores. The ARCHES trial, however, did not show any difference in HRQoL between ADT + enzalutamide and ADT alone over two years. For ADT + apalutamide, no difference in HRQoL was seen compared to ADT alone. No data on HRQoL was available for treatment with ADT + radiotherapy.

For PFS, we found a statistically significantly longer time to progression for all systemic mHSPC treatments compared to ADT alone. Novel hormonal treatments had a statistically significantly stronger effect than ADT + docetaxel, but no statistically significant difference was identified between hormonal treatments.

Regarding AEs, our analyses showed a statistically significant increase in any grade AEs for ADT + docetaxel compared to ADT alone, primarily driven by higher incidence rates of grade 3-5 AEs. This increase in AEs is explained by the acute effects of chemotherapy over the first months of treatment. For ADT + abiraterone, we found a lower incidence of grade 1-2 AEs, but a higher incidence of grade 3-5 AEs than for ADT alone, resulting in a comparable incidence of any grade AEs. For both ADT + enzalutamide and ADT + apalutamide, no statistically significant difference in AE rates was observed versus ADT alone. Only limited data was available for ADT + radiotherapy, which showed similar grade 3-5 AE rates as for ADT alone. It is important to note that the studies were not powered to evaluate differences in AE incidence rates, with studies on ADT + docetaxel and ADT + abiraterone reaching higher precision and thus more likely to find a statistically significant difference. Furthermore, the comparison between different treatments relies on the assumption that AE incidences are constant over time, which may be in disfavour of ADT + docetaxel. And last, the standard co-treatment of prednisone with ADT + abiraterone has to be considered as an additional factor that may influence the comparison across treatments.

In summary, our assessment of the clinical effectiveness showed that ADT + docetaxel, ADT + abiraterone, ADT + enzalutamide and ADT + apalutamide all seem to be effective in improving survival in newly diagnosed mHSPC patients. We further showed a survival benefit with ADT + radiotherapy among low-volume *de novo* mHSPC patients. While we found no statistically significant benefit of one systemic mHSPC treatment over another, novel hormonal treatments generally appeared to have a greater survival benefit and had a statistically significantly greater effect on PFS compared to ADT + docetaxel. Improved longer-term HRQoL was shown for ADT + abiraterone compared to ADT alone, while ADT + docetaxel appeared to lead to a short-term HRQoL decline but improved preservation of HRQoL in the longer term over ADT alone. No consistent effect on overall HRQoL was found for ADT + enzalutamide and ADT + apalutamide compared to ADT alone. Furthermore, our evaluation of AEs showed higher rates of severe AEs for ADT + docetaxel and ADT + abiraterone compared to ADT alone, while the AE incidence appeared lower for ADT + enzalutamide and ADT + apalutamide. More detailed data on HRQoL and AEs within and across patient subgroups would be necessary to better judge the relative effectiveness of treatments for these important outcomes.

Benefit-Harm Assessment

In the benefit-harm assessment, 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, with a probability for a net clinical benefit of 97.5%, 83.3%, and 89.4%, respectively. Meanwhile, the benefits of ADT + docetaxel were much less likely to outweigh the harms of treatment, with a 14.9% probability for a net clinical benefit. The unfavourable benefit-harm balance for ADT + docetaxel was partly due to the lower relative risk reduction of death, but was mainly driven by the higher rates of AEs, which offset the benefit.

We conducted several sensitivity analyses, which did not result in different conclusions. Using a longer time horizon of 60 months, we observed a higher probability for a net clinical benefit compared to a time horizon of 24 months for all treatments, with a probability for net benefit of 92.0% for ADT + abiraterone, 91.3% for ADT + enzalutamide, 98.0% for ADT + apalutamide. The benefit-harm balance for ADT + docetaxel remained unfavourable with a probability for a net clinical benefit similar to that at 24 months (15.1%). While the increase in probability for a benefit was only negligible, the absolute net clinical benefit showed a larger increase with the longer time horizon. As such, the number of prevented death-equivalents increased from 17 at 24 months to 36 per 1,000 at 60 months in patients treated with ADT + abiraterone. Similarly, the net prevented death-equivalents increased from 45 at 24 months to 80 per 1,000 patients at 60 months treated with ADT + enzalutamide, and from 46 per 1,000 patients treated with ADT + apalutamide at 24 months to 90 per 1,000 patients at 60 months, respectively. However, we found that patients treated with ADT + docetaxel rather experienced net harms, corresponding to 254 death-equivalents in 1,000 mHSPC patients at 24 months and 169 in 1,000 patients at 60 months.

In a further sensitivity analysis we assumed substantially lower preference weights for AEs; that is, that patients are far less concerned about AEs than in the main analysis. This analysis resulted in a more favourable benefit-harm profile for all treatments, with both a higher net clinical benefit and a higher probability of experiencing a net clinical benefit. However, ADT + docetaxel still did not exceed the probability threshold for a net clinical benefit (16.4%).

We also explored the sensitivity of the results to using different data inputs in the model. When omitting the evidence from GETUG-AFU 15, CHAARTED, LATITUDE, and ENZAMET, the probability for a net clinical benefit was comparable to the analysis based on the full evidence for ADT + abiraterone, while the probability for a net clinical benefit was relevantly lower for both ADT + docetaxel (2.5% vs. 14.9%) and ADT + enzalutamide (78.3% vs. 89.4%). Thus, while ADT + enzalutamide showed a net clinical benefit overall, the benefit-harm balance was dependent on judgement about the appropriateness of including the data from ENZAMET. In another sensitivity analysis that assumed much higher incidence rates for death based on pooled reconstructed data from the economic analysis, the BHA showed a more substantial net clinical benefit with all treatments, with almost twice the net clinical benefit compared to the main analysis.

Overall, the BHA indicated the highest probability for a net clinical benefit with ADT + apalutamide, followed by ADT + abiraterone and ADT + enzalutamide. While the ranking of

these novel hormonal treatments slightly varied across sensitivity analyses, ADT + docetaxel consistently ranked last and did not reach the probability threshold for a net clinical benefit (i.e., 60%) in any of the analyses. However, it is worth noting that this assessment is among the first BHAs conducted in the context of mHSPC, and there is little evidence for comparison. Therefore, our results should be interpreted with caution and need to be considered in light of the limitations of the study, such as 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. As such, the evidence from the BHA should be considered as complementary evidence to the other, standard components of this HTA.

Health Economic Literature Review

Out of a total of 1,799 citations identified from the electronic database searches, eleven were eligible cost-effectiveness analyses including patients diagnosed with mHSPC. Among the identified studies, four were from China/Hong Kong, three from North America (USA or Canada), two from Brazil, one from the UK, and one from Spain. Six studies compared the combination of ADT + docetaxel with ADT treatment alone [Aguiar 2017, Beca 2019, Garcia 2017, Woods 2018, Zhang 2017, Zheng 2017], and four studies compared ADT + abiraterone with ADT + docetaxel or ADT alone [Aguiar 2019, Chiang 2019, Ramamurthy 2019, Sathianathen 2019]. One study, while focusing on maximum androgen blockade (through flutamide and bicalutamide + ADT), also provided a comparison of ADT + docetaxel and ADT alone [Liu 2019]. No study investigating the cost-effectiveness of ADT + enzalutamide, ADT + apalutamide, or ADT + radiotherapy was identified. The adopted perspectives, time horizons, and types of costs considered in the analyses were heterogeneous.

According to the CHEERS checklist, the quality of reporting differed substantially between the eleven eligible studies. Since three studies missed to report very 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 eleven cost-effectiveness studies were considered.

The ICERs of ADT + docetaxel compared to ADT alone ranged from USD 4,033 to USD (Woods 2018, lifetime horizon) to USD 50,489 (Ramamurthy 2019, 3-year time horizon). The ICERs of ADT + abiraterone compared to ADT + docetaxel ranged from USD 295,212 (Sathianathen 2019, lifetime horizon) to USD 1,009,975 (Ramamurthy 2019, 3-year time horizon). Finally, the ICERs for ADT + abiraterone compared to ADT alone ranged from USD 188,085 (Chiang 2009, lifetime horizon) to USD 415,063 (Ramamurthy 2019, 3-year time horizon).

Cost-Effectiveness Analysis

Over a 15 year time horizon, we estimated in the base case analysis of our cost-effectiveness model that 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. The resulting ICER was CHF 18,124 per QALY gained.

ADT + apalutamide was estimated to be a dominated strategy (i.e. generating higher costs and lower QALYs relative to comparators). We found ADT + abiraterone and

ADT + enzalutamide resulted in high ICERs above CHF 100,000 per QALY gained (CHF 294,163/QALY for ADT + abiraterone vs. ADT + docetaxel, CHF 1,066,633/QALY for ADT + enzalutamide vs. ADT + abiraterone).

For all novel hormonal mHSPC treatments, the most substantial cost components 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.

In deterministic sensitivity analyses, variation in utility values pre-progression, in intervention treatment effect sizes (HRs), and in proportion of patients on subsequent lines of treatment after the first progression impacted the ICER most. Nevertheless, all ICERs in the deterministic sensitivity analyses comparing ADT + docetaxel with ADT monotherapy were below CHF 25,000 per QALY gained. For comparisons of ADT + abiraterone vs. ADT + docetaxel, the ICERs were always estimated above CHF 100,000 per QALY gained.

In a few scenarios, ADT + enzalutamide became dominated as ADT + apalutamide. For example, when excluding LATITUDE and ENZAMET in the estimation of treatment effects (HRs) and when restricting the time horizon to 5 years. Except for variations in drug prices, almost all remaining scenarios had a moderate to minor impact on the model results.

In summary, we conclude from the cost-effectiveness analysis that the ICER of ADT + docetaxel vs. ADT has a point estimate of CHF 18,124 and is most likely below CHF 100,000 per QALY gained, whereas the treatment strategies involving novel hormonal treatments are likely above this value at current prices.

Budget Impact Analysis

Taking into consideration the growth and ageing of the Swiss population, it has been 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 results of the budget impact analysis suggested that the total costs of mHSPC cases in Switzerland strongly depend on the treatment strategy. ADT alone (CHF 35.7 million) and ADT + docetaxel (CHF 46.3 million) were less expensive than ADT + abiraterone, ADT + enzalutamide, or ADT + apalutamide (more than CHF 150 million in 2020). The costs of treatment combinations strongly depended on the assumed proportional use. For example, assuming that 50% of the eligible patients would be treated with ADT alone, 25% with ADT + docetaxel, and 25% with ADT + abiraterone led to total costs of CHF 70.9 million in 2020 (i.e. CHF 35.2 million more than treating with ADT alone). According to expert opinion, it is very difficult to estimate how mHSPC patients in Switzerland are currently treated (i.e., which percentage receives which treatment). Nevertheless, it appears evident 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.

Conclusion

In this HTA, we comprehensively evaluated the clinical effectiveness, safety, benefit-harm balance, and health economic characteristics of docetaxel, abiraterone, enzalutamide, and apalutamide in combination with ADT among each other and compared to ADT alone in patients with newly diagnosed mHSPC. The assessment of the clinical efficacy and safety additionally included an evaluation of radiotherapy in combination with ADT compared to ADT alone.

In the assessment of clinical efficacy and safety, we found that docetaxel, abiraterone, enzalutamide, and apalutamide in combination with ADT all provide a relevant survival benefit in newly diagnosed mHSPC patients compared to ADT alone. Meanwhile, none of the systemic combination treatments was significantly more effective in prolonging survival than the others. Furthermore, we found radiotherapy to be effective in *de novo* low-volume mHSPC patients. Evidence related to HRQoL indicated a benefit primarily for ADT + abiraterone, and a short-term HRQoL decline with improved longer-term HRQoL preservation for ADT + docetaxel. No difference in HRQoL was observed for ADT + enzalutamide or ADT + apalutamide. Both ADT + docetaxel and ADT + abiraterone were associated with higher incidence of grade 3-5 AEs compared to ADT alone, while no statistically significant differences in grade 3-5 AEs were observed for ADT + enzalutamide and ADT + apalutamide compared to ADT alone.

In the BHA, we assessed the benefit-harm balance of systemic mHSPC treatments from a clinical decision-making perspective using a 2-year time horizon. We found a high probability for a net clinical benefit for ADT + abiraterone, ADT + enzalutamide and ADT + apalutamide compared to ADT alone. Meanwhile, the probability for a net clinical benefit was low for ADT + docetaxel relative to ADT alone. More detailed reporting of HRQoL-related outcomes and AEs by the RCTs could aid a more detailed assessment in these dimensions, as well as the conduct of a more comprehensive BHA. This analysis focused mainly on the evaluation of the benefit-harm balance from a clinical decision-making perspective, without taking any cost factors into account. Since the BHA pursues a different aim, its results thus should not be interpreted interchangeably but rather as complementary to the cost-effectiveness results.

In the cost-effectiveness analysis, we related the clinical benefits of the systemic mHSPC treatments to their costs using a 15-year time horizon from a Swiss healthcare payer perspective. Our results suggested that ADT + docetaxel is a cost-effective treatment option (ICER of CHF 18,124 per QALY gained relative to ADT) in Switzerland. We found ADT + apalutamide to be a dominated strategy, and both ADT + abiraterone and ADT + enzalutamide resulting in ICERs above CHF 100,000 per QALY gained (CHF 294,163/QALY for ADT + abiraterone vs. ADT + docetaxel, CHF 1,066,633/QALY gained for ADT + enzalutamide vs. ADT + abiraterone). This is due to the fact that costs for novel

hormonal therapies are relatively high in comparison to the costs of chemotherapy. This was also reflected in the BIA, suggesting that treatment strategies mainly based on ADT alone or ADT + docetaxel led to the lowest total costs, ranging from CHF 35.7 million for ADT alone to CHF 46.3 million for ADT + docetaxel in 2020. Alternative assumptions considering the use of novel hormonal treatments led to significantly higher total costs.

In conclusion, none of the combination treatments clearly performed better than the others across all evaluated dimensions. We found all evaluated combination treatments to be effective options for prolonging survival in men with newly diagnosed mHSPC, with longer-term advantages in quality of life for ADT + abiraterone and ADT + docetaxel. 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 is the only cost-effective treatment option from a Swiss healthcare payer perspective based on current drug prices. Novel hormonal therapies are associated with relevantly increased costs for the healthcare system. All these factors need to be considered jointly when making recommendations for the treatment of newly diagnosed mHSPC in Switzerland.