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

Executive Summary

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Executive Summary

Prostate cancer is the most frequent cancer in men. Progression is relatively slow, especially when tumors are 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 to treat mHSPC, including systemic chemotherapy (docetaxel), second generation non-steroidal anti-androgen therapies (abiraterone, enzalutamide, apalutamide), and/or radiotherapy, which all may be added to ADT. The optimal treatment strategy, however, remains unclear.

The Swiss Medical Board assessed whether adding 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, 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 ADT + docetaxel and would be large if all patients received ADT + a novel hormonal therapy.

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 and *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	Net 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 is 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