Single Technology assessment

IDnr 2018_034: Enzalutamide (Xtandi) in high-risk non-metastatic castration resistant prostate cancer patients (nmCRPC)

21-08-2019

Norwegian Medicines Agency

PREFACE

Implementation of the National System for the introduction of new technologies in the specialist healthcare system will help ensure that assessment of appropriate new technologies happens in a systematic manner with respect to efficacy and safety, as well as impacts on health and society. The main aim of the new system is described in the National Health and Care Plan 2011-2015 and the White Paper 10 (2012-2013), Good quality - safe services. The regional health authorities, the Norwegian Knowledge Centre for Health Services, the Norwegian Medicines Agency and the Directorate of Health collaborate on tasks related to the establishment and implementation of the new system. Eventually, the National System for the introduction of new technologies in the specialist healthcare system will assist in the rational use of health care resources.

The Norwegian Medicines Agency has been assigned the responsibility to evaluate Single Technology Assessments (STA) of individual pharmaceuticals. A Single Technology Assessment is a systematic summary of evidence based on research on efficacy, safety and impact assessment. For pharmaceuticals, this will usually revolve around budgetary consequences or resource allocation. The burden of proof relating to the documentation of efficacy, safety and cost-effectiveness is borne by the MA-holder for the pharmaceutical under review. NoMA can, when necessary, provide guidance to pharmaceutical companies.

NoMA assesses the submitted evidence for all important clinical outcomes, resource use as well as the assumptions made in the analysis presented by the MA-holder and the presented results. NoMA does not perform its own health economic analyses. If required, NoMA may request additional information and perform additional calculations of the costs and cost effectiveness using the submitted model.

NoMA evaluates the relative efficacy and incremental costs in relation to a relevant comparator. The cost-effectiveness ratio will be weighed against the severity of the relevant condition/disease. NoMA does not assess the benefit risk balance already assessed under the market-authorisation procedure. Information about this is provided by EMA (SmPC Xtandi).

Single Technology Assessment of pharmaceuticals is intended to support sound decision making on potential introductions of new technologies, and prioritisation made at the Health Authority level. NoMA has no decision-making authority in this system.

All assessments are published and available to the public (www.legemiddelverket.no).

NORWEGIAN SUMMARY

Scope
This report is a report regarding use of enzalutamide (Xtandi) for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). It is based on the FINOSE-report, where the relative effectiveness and the health economic model is discussed. In addition a cost analysis and budget consequences have been performed nationally.

Patient number in Norway
The patient population consist of patients with nmCRPC who are at high-risk of disease progression in good performance status. Estimated number of patients eligible for treatment with enzalutamide in non-metastatic stage is 75 patients per year.

Severity and absolute shortfall
FINOSE considers high-risk nmCRPC to be a severe disease because of the high-risk of progression to metastatic setting. The absolute shortfall may affect whether the cost are considered to be in reasonable relationship to the utility of the treatment. NoMA has not calculated the absolute shortfall because of the immature overall survival (OS) data.

Treatment in Norwegian clinical practice
The current standard treatment for high-risk nmCRPC is androgen deprivation therapy (ADT) alone. Enzalutamide is currently offered to patients with mCRPC. In both the nmCRPC and mCRPC indication patients are treated until disease progression and ADT is continued.

Effectiveness documentation
The effectiveness documentation is derived from the study PROSPER, a global phase III placebo-controlled study evaluating enzalutamide in patients with high-risk nmCRPC. In PROSPER treatment with enzalutamide + ADT were associated with statistically significant improvement in metastases-free survival (MFS) versus placebo + ADT. However the data for OS is still immature and no clear separation between the two curves can be seen.

Safety
The safety profile for enzalutamide in PROSPER trial was consistent with that reported in previous clinical trials involving men with CRPC. The most common adverse reactions reported were fatigue, hot flushes, nausea, fractures and hypertension.

Cost-effectiveness
The FINOSE's main critique against the health economic model of the company is that it assumes that life is prolonged when treating with enzalutamide + ADT in the non-metastatic stage compared to when treating with enzalutamide + ADT in the metastatic stage. At this time point data from the clinical trial

PROSPER shows no survival gain for enzalutamide used in the non-metastatic stage. This implies that the documented health gain is minimal, while treatment duration and therefore treatment cost with enzalutamide in the non-metastatic stage is significantly higher than in the metastatic stage.

Budgetary consequences

Based on the company's budget impact analysis, budgetary consequences will be about [redacted] NOK in a stable market with maximum retail price. The budgetary calculations are uncertain and simplified.

Please see appendix 2

Norwegian Medicines Agency, 21-08-2019

Elisabeth Bryn
Head of unit

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Assessor

LOGG

Bestilling:	*ID_nr 2018_034: Enzalutamid (Xtandi) til behandlng av ikke-metastatisk kastrasjonsresistent prostatakreft*
Forslagstiller:	Statens Legemiddelverk
Legemiddelfirma:	Astellas
Preparat:	Xtandi
Virkestoff:	Enzalutamid
Indikasjon:	Xtandi er indisert til: - Behandling av voksne menn med høyrisiko ikke-metastatisk kastrasjonsresistent prostatakreft (CRPC)
ATC-nr:	L02BB04

Prosess

Dokumentasjon bestilt av Legemiddelverket	17-04-2018
Fullstendig dokumentasjon mottatt hos Legemiddelverket	10-12-2018 (FINOSE-del) 08-07-2019 (Nasjonal del)
Klinikere kontaktet for første gang	22-01-2019
Rapport ferdigstilt:	21-08-2019
Saksbehandlingstid:	FINOSE-rapport: 165 dager hvorav 91 dager i påvente av ytterligere opplysninger fra legemiddelfirma. Dette innebærer en reel saksbehandlingstid hos legemiddelverket på 74 dager. Nasjonal del: 44 dager.
Saksutredere:	Helle Endresen Effekt og modell ble utredet i samarbeid med TLV og FIMEA. Se vedlagt FINOSE rapport
Kliniske eksperter:	Karol Axcrona Arne Berg David Robinsson

Kliniske eksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). Legemiddelverket er ansvarlig for rapportens innhold. Kliniske eksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten.

APPENDIX 1: FINOSE REPORT

Please see attached report

APPENDIX 2: NATIONAL PART

1.1 COST ANALYSIS

The company has developed a simplified cost analysis in addition to the submission sent in through FINOSE. The purpose of the economic analysis is to give an estimate of the treatment cost with enzalutamide. The analysis delivered by the company focus on the difference in cost between the two scenarios where enzalutamide is given either early in nmCRPC or later in metastatic setting, since in both cases the treatment is continued until disease progression (or intolerable toxicity), the treatment duration may differ between the arms. Subsequent treatment is not included in the analysis and cost consist of the cost of enzalutamide only.

For estimating duration of treatment in both scenarios (enzalutamide given in nmCRPC or in mCRPC) a Markov model was established. The Markov states captures initiation and duration of enzalutamide treatment for a patient in each of the scenarios see figure 1. Transition between Markov states were estimated using individual patient data from the enzalutamide clinical program. The source of data for enzalutamide in nmCRPC is the pivotal trial PROSPER (1). Data on use of enzalutamide in mCRPC (patients with metastases not yet indicated for chemotherapy) is available in the pivotal trial PREVAIL (2). Both studies studied disease progression; MFS in PROSPER and PFS in PREVAIL. Furthermore, time to treatment discontinuation (TTD) was estimated in both trials.

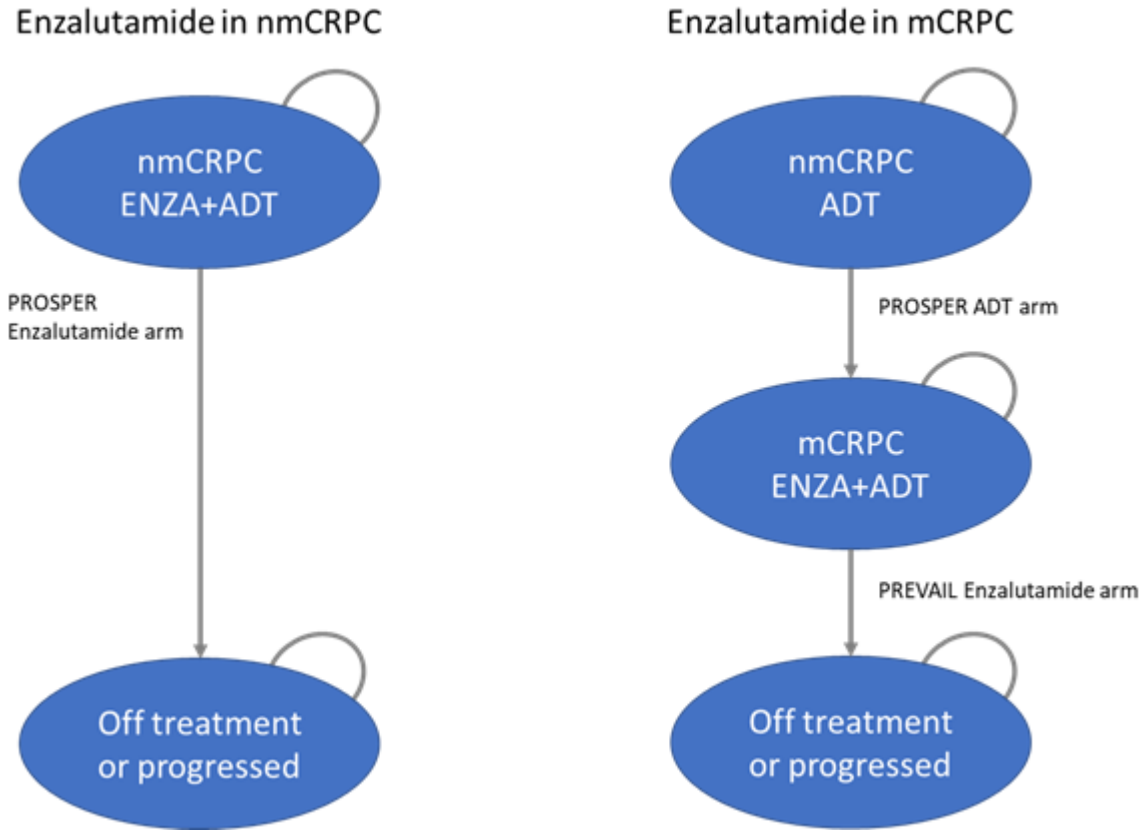

Figure 1: Markov states and source of transition data

The cycle length assumes 13 cycles per year á 28 days (364 days per year). This was selected to measure the number of packs prescribed where one pack is equivalent to 28 days of treatment at standard dose.

Statistical analyses duration data

Transition probabilities for moving between states were estimated based on either time to progression (MFS or PFS) data or TTD data from the pivotal trials PROSPER and PREVAIL. Kaplan-Meier (KM) curves were tested for proportional hazard using statistical testing and visual inspection of log-cumulative hazard plots. A number of parametric survival functions were estimated. Selection of best model fit was based on Akaike information criteria (AIC) and Bayesian information criteria (BIC). Furthermore, visual inspection was carried out by plotting the projected survival curves overlaid with the KM survival functions. Finally, model goodness of fit was assessed based on clinical plausibility of the proportion of patients estimated to be surviving at the tails of the curve was examined and discussed with a medical oncologist. For extrapolation in nmCRPC the consulted clinical expert confirmed that none of the six standard parametric models provided a reasonable fit and/or extrapolation of the data and that the spline model (2 knots, hazard scale) provided much more plausible extrapolations.

Table 1: The base case assumption

Patient group	Base case
nmCRPC	TTD spline (k=2, hazard)
mCRPC	TTD (log-normal)

Drug wastage is included in the cost of medication. One pack covers the recommended dosing for 28 days (1 cycle). The full cost of one pack is added in the start of each cycle for patients actively treated with enzalutamide. This means that if patients discontinue during a cycle, any unused medication is considered wasted.

Results

The table under shows the average annual cost per patients over the 5-year time horizon.

Table 2: Average cost per patient per year (PSP incl VAT)

	Number of packages per year	Annual cost per patient*
Enzalutamide in high risk nmCRPC	8.1	268,907
Enzalutamide in mCRPC	4.6	154,264
Difference	**3.4**	**114,643**

* Undiscounted.; Pharmacy Selling Price including VAT; 5-year horizon

NoMA discussion

NoMA requested a simplified cost analysis for the treatment cost of enzalutamide. The cost analysis estimates a higher cost in non-metastatic versus metastatic setting, this is plausible. The cost analysis have some shortcomings when it comes to the opportunity to choose extrapolation-curve. As stated in the FINOSE report, there is a large uncertainty regarding the extrapolation of MFS and hence it will be for TTD.

1.2 BUDGETARY CONSEQUENCES

The impact of introducing enzalutamide as standard treatment in high-risk nmCRPC was calculated using a 5-year budget impact model. A cohort of patients start treatment each year. In line with the cost-analysis, it is assumed that each cohort of patient starting treatment in a given year will stay on treatment for an average until progression. Patients on the standard treatment arm will start on treatment when metastases develop. Treatment duration (and time to developing metastases) are estimated using the same Markov model as the net-present cost. For each arm, the costs are accrued for up to year 5. The budget impact in year X is captured as the sum in year X. Costs in the budget impact are not discounted.

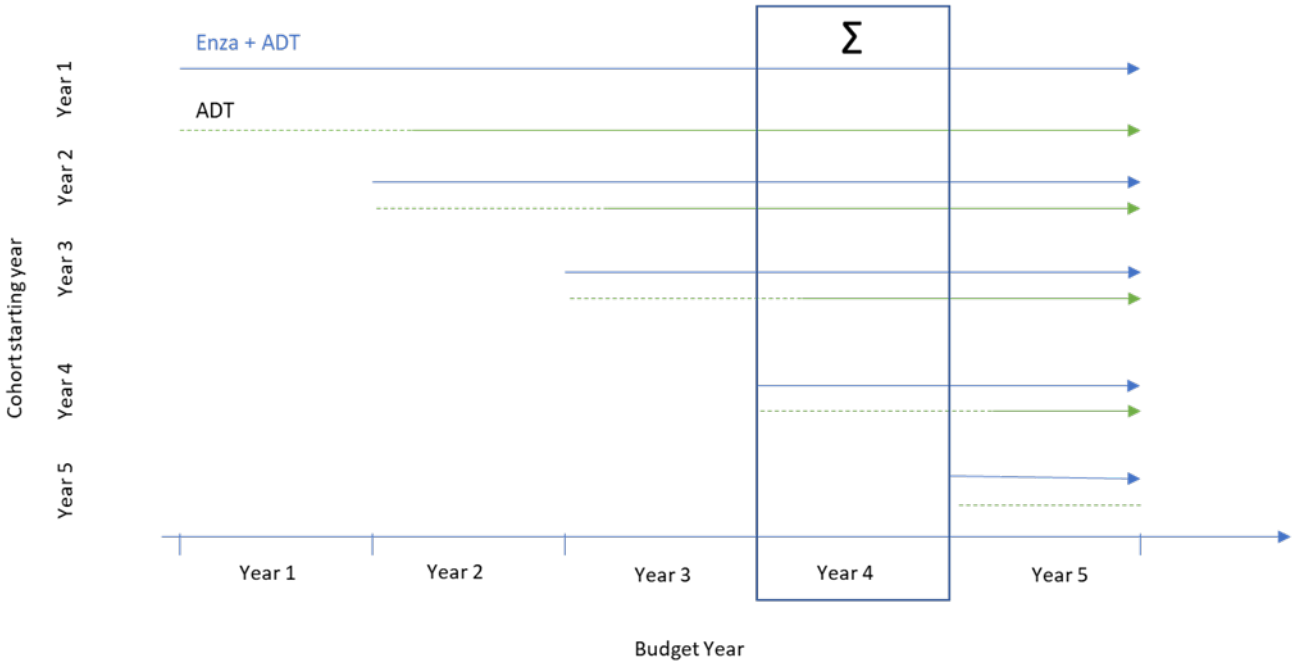

Figure 1: Illustration of budget impact model

The incidence of mCRPC is assumed to be 1000 (using average number of prostate cancer deaths per year as an approximation of incidence). Assuming that 15% of these patients will be diagnosed in the nmCRPC state and 50% of these are at high-risk of progression, the annual number of eligible high-risk nmCRPC patients would be (1000×15%×50%) = 75 patients per year

Uptake in the group of eligible patients is assumed to be [redacted] If enzalutamide is not adopted for use in nmCRPC, all patients will be treated according to standard of care.

Table 4: Uptake of enzalutamide in nmCRPC and estimation of patients

[redacted]

Results

Table 5 shows the results of the base case budget impact analysis.

Table 5: Estimated budget impact at pharmacy selling prices incl. VAT

NoMA discussion

The budget impact calculated by the company shows an increase in the sales of enzalutamide if used in non-metastatic setting. The estimated patient number seems reasonable and clinical experts agree on the number of patient likely to be eligible for treatment with enzalutamide in non-metastatic setting. The introduction of enzalutamide for non-metastatic prostate cancer will involve some reduced sales of enzalutamide in the metastatic setting due to treatment in the non-metastatic setting is longer than in the metastatic setting. NoMA has not detailed gone through the budget impact analysis delivered by the company.

REFERENCES

1. Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. The New England journal of medicine. 2018;378(26):2465-74.
2. Beer TM, Tombal B. Enzalutamide in metastatic prostate cancer before chemotherapy. The New England journal of medicine. 2014;371(18):1755-6.