FINOSE Joint HTA
Fimea NoMA TLV

FINOSE joint assessment report

Xtandi (enzalutamide)

Assessed indication
Enzalutamide for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer

Case number Norwegian Medicines Agency: 18/14686
Case number TLV: 2610/2018
Case number Fimea: 006120/12.01.01/2018

Preface

The FINOSE is a Nordic collaboration between Finland, Norway and Sweden in HTA (Health Technology Assessment). The collaborating agencies are Sweden's Dental and Pharmaceutical Benefits Agency (TLV), the Norwegian Medicines Agency (NoMA) and the Finnish Medicines Agency (Fimea).

The agencies aim to make joint assessments of medicines, for both relative effectiveness and health economics.

The FINOSE collaboration is not aiming for joint decision making.

In this FINOSE report, TLV and NoMA acted as authors and Fimea had a reviewer role.

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Summary

- Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses despite castrate levels of testosterone.
- Non-metastatic castration resistant prostate cancer (nmCRPC) is defined as CRPC with no detectable bone or visceral metastases on computed tomography (CT) and/ or magnetic resonance imaging scans (MRI).
- Since earlier Xtandi is indicated for treatment of CRPC in the metastatic setting. This assessment covers the indication for the treatment of adult men with high-risk nmCRPC.
- FINOSE considers high-risk nmCRPC to be a severe disease because of the high-risk of progression to metastatic setting.
- Xtandi is a potent androgen receptor signaling inhibitor that blocks several steps in the androgen receptor signalling pathway. Xtandi treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumor regression.
- FINOSE assesses that the comparative treatment used by the company in its clinical phase III trial (PROSPER), androgen deprivation therapy (ADT) + placebo, is a relevant comparative treatment option.
- In PROSPER treatment with Xtandi + ADT were associated with statistically significant improvement in metastases-free survival (MFS) versus placebo + ADT. However, the data for overall survival (OS) is still immature and no clear separation between the two curves can be seen. It is not possible to assess whether moving Xtandi forward in the treatment algorithm for prostate cancer could provide benefit in life expectancy.
- From the PROSPER trial, Xtandi seems to be well tolerated and the safety profile appears similar to that reported in previous Xtandi clinical trials.
- In order to analyse the cost-effectiveness of treating patients with high-risk, nmCRPC the company compares Xtandi in addition to ADT with ADT alone in terms of cost and health effects in an health economic model which extrapolates data mainly from the PROSPER trial. Patients who were treated with ADT in the non-metastatic phase are assumed to be treated with Xtandi+ADT in the metastatic stage.
- FINOSE´s main critique against the health economic model of the company is that it assumes that life is prolonged with a year when treating with Xtandi+ADT in the non-metastatic stage compared to when treating with Xtandi+ADT in the metastatic stage. Since treatment duration, and therefore treatment cost, with Xtandi in the non-metastatic stage is significantly higher than in the metastatic stage, cost-effectiveness in the non-metastatic stage can be hard to conclude depending on prices in the different countries.

The conclusions in the report can be changed if the prerequisites the assessment is based upon will differ in an important way.

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1 Scope

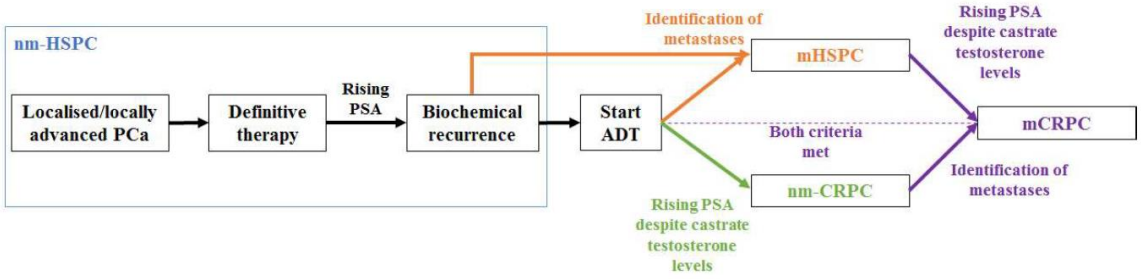
This single technology assessment (STA) concerns the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC). The FINOSE assessment is primarily based on the documentation presented by Astellas Pharma.

2 Background

2.1 Non-metastatic castration-resistant prostate cancer (nmCRPC)

Prostate cancer begins when cells in the prostate gland start to grow uncontrollably. Patients with localised prostate cancer may receive radical prostatectomy or radiotherapy. If not eligible for these options they may receive androgen deprivation therapy (ADT). Stages that are responsive to ADT are referred to as hormone-sensitive prostate cancer (HSPC). As the disease progresses ADT becomes less effective, at which point serum prostate-specific antigen (PSA) levels begin to rise. Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses despite castrate levels of testosterone while on treatment with a luteinizing-hormone releasing hormone analogue (LHRHa), or following bilateral orchiectomy [1].

A proportion of patients who progress to CRPC after local treatment do not have detectable metastases, non-metastatic CRPC (nmCRPC). In the majority of patients, mCRPC evolves from nmCRPC. PSA doubling time has been shown to be a strong predictor of the development of metastases in these patients [2, 3]. Thus, PSA doubling time (PSADT) is reported as a useful prognostic factor in identifying patients at high-risk of development of clinically detectable metastatic disease. According to the guidelines from the European Association of Urology (EAU) approximately one-third of men with nmCRPC with rising PSA will develop bone metastases within 2 years [4].



ADT: androgen deprivation therapy, CRPC: castration-resistant prostate cancer, HSPC: hormone-sensitive prostate cancer, m: metastatic, nm: non-metastatic, PCa: prostate cancer, PSA: prostate-specific antigen

Figure 1: Stages of prostate cancer for those diagnosed at non-metastaic stage [5].

Prostate cancer remains the second most commonly diagnosed cancer in men, with an estimated 1,1 million diagnoses worldwide in 2012, accounting for 15 % of all cancers diagnosed [6]. According to NORDCAN (a database of cancer statistics for the Nordic countries) approximately 10 000 men are diagnosed yearly with prostate cancer in Sweden and on average 2 400 men die yearly due to prostate cancer. The corresponding estimates for Norway are approximately that 5 000 men diagnosed annually and about 1 000 men die yearly due to their disease. More than 100 000 Swedes and 50 000 Norwegians live with prostate cancer. For the vast majority the cancer is local/locally advanced and the majority of these patients may live with their cancer for decades. It is estimated that patients with CRPC account for around 20 % of all prostate cancer cases, and amongst the population with CRPC, between 10-20 % have non-metastatic disease. The share of nmCRPC patients will depend on the access to and use of modern diagnostic imaging [7, 8].

2.2 Treatment with Xtandi

Xtandi received marketing authorisation in Europe through centralised procedure in June 2013 for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy. Subsequently, Xtandi has received extension of the indication to include two more indications.

2.2.1 Therapeutic indication

Xtandi is indicated for:
- the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).
- the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

This assessment covers the first part of the indication.

2.2.2 Mechanism of action

Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signaling. Despite low or even undetectable levels of serum androgen, androgen receptor signaling continues to promote disease progression. Stimulation of tumour cell growth via the androgen receptor requires nuclear localisation and DNA binding. Xtandi is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Xtandi competitively inhibits androgen binding to androgen receptors, and consequently; inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Xtandi treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression.

2.2.3 Posology and method of administration

The recommended dose is 160 mg enzalutamide (four 40 mg soft capsules) as a single oral daily dose. Xtandi is for oral use and the capsules should be swallowed whole with water, and can be taken with or without food.

Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

If a patient experiences a ≥ grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

2.3 Treatment of nmCRPC and severity of disease

2.3.1 Treatment guidelines

There is no standard of care for the management of nmCRPC due to the heterogeneity of the disease entity, with some men exhibiting indolent, slow growing process while others experience a more rapid progression and development of metastases. Although continued use of ADT is part of clinical practice, no therapy is approved specifically for the treatment of patients with nonmetastatic CRPC or for prevention of metastasis. Guidelines for CRPC are available only

for metastatic cases in Finland. For patients with nmCRPC treatment is individualised according to the patient and the disease in Finland and available alternatives are follow-up, radical therapies and hormonal treatment.

Treatment guidelines from Sweden (Cancercentrum, [9]) states that patients with nmCRPC should be monitored every 3 months and enrolled in a clinical trial if possible. Patients who cannot be enrolled in a clinical trial, can be considered for treatment with bicalutamide. Treatment with bicalutamid may lower PSA but often only moderate levels and for a couple of months in approximately one third of the patients.

The Norwegian guidelines (Nasjonalt handlingsprogram prostatkreft [10]) originate back to 2015 and are currently under revision.These guidelines recommend observation and continuous ADT. In general both Norwegian and Swedish clinical experts agree on that, but also state that treatment is often individualised and the wide use of MRI and PET nowadays, would shift many patients from a non-metastatic state to a metastatic state, or detect lesions that can be treated with local therapies.

Table 1: Current treatment pathway for prostate cancer

	Hormon sensitive	Hormon relapsed		
Non-metastatic	• ADT • Radical therapy (surgery or radiotherapy)	• ADT • Xtandi + ADT		
Metastatic	• ADT • Docetaxel + ADT • Zytiga + ADT (not reimbursed in Norway, restricted reimbursement in Sweden to patients intolerant to docetaxel)	<u>Chemotherapy not yet indicated</u> • Zytiga • Xtandi • Watchful waiting	<u>Chemotherapy indicated</u> • Docetaxel	<u>Post-docetaxel</u> • Zytiga • Xtandi • Jevtana • Xofigo* *bone metastasis only

2.3.2 Comparator

The company has chosen ADT as a comparator. The choice was supported by literature review, Swedish/Norwegian PICO assessment prior to the FINOSE application and different European clinical guidelines for nmCRPC.

FINOSE discussion

As mentioned above observation plus continuous treatment with ADT is a relevant comparator for both Finland, Norway and Sweden for the general population with nmCRPC. This is supported both by the Swedish and Norwegian clinical guidelines and expert statements. None of the guidelines (European, Norwegian or Swedish) recommend any specific treatment for patients with high-risk nmCRPC.

One could argue that bicalutamide might be a relevant comparator, but as the use of it is limited and the duration of treatment it is only for a short time, it is not suggested as a relevant comparator from clinical experts.

FINOSE conclusion: FINOSE finds that it is reasonable to assume that the relevant comparator is continuous treatment with ADT. This is also in line with what the company has claimed and it is supported by clinical experts.

2.3.3 Severity of the disease

Men with CRPC can have metastatic or non-metastatic disease. Development of metastases is associated with potentially serious complications for patients and their mortality rates increase substantially. Health-related quality of life (HRQoL) of patients deteriorate upon the development of metastases and the symptom burden that is initially low in these patients increases with the development of metastases. Many patients who progress to metastatic stage are diagnosed with bone metastases. These patients often experience bone pain and fractures, while patients often are asymptomatic during the nmCRPC stage. In the pivotal phase III trial PROSPER men with nmCRPC had relatively good HRQoL.

The degree of severity can affect whether the costs are considered to be in reasonable proportion to the benefit of the treatment. In this assessment it is not possible to calculate the degree of severity with a quantitative method because the health economic model is not suitable to estimate the prognosis for the ADT arm considered by FINOSE to be the most plausible.

FINOSE conclusion: Patients with nmCRPC have generally high HRQoL as most of these patients are asymptomatic during this stage. When the disease progresses patients HRQoL deteriorates. Patients with high-risk nmCRPC are patients whose cancer has not metastasised yet, but they will eventually develop metastases. TLV and NoMA have previously classified mCRPC as a disease with high severity. Based on this FINOSE considers nmCRPC to be a severe disease.

2.4 Clinical efficacy and safety

2.4.1 Enzalutamide efficacy studies

The clinical trial program for Xtandi consists of a large phase III study (PROSPER) [11] and a smaller phase II study (STRIVE) [12]. STRIVE included only a sub-population of patients with nmCRPC, see table 2 for overview of the study program.

Table 2: Overview of clinical studies

Study	PROSPER (MDV3100-14) [11]	STRIVE (MDV3100-09) [12]
Study design	Phase 3, randomised, double-blind, placebo-controlled, multinational	Phase 2, randomised, double-blind, active-controlled
Population	Patients with high-risk (baseline PSA levels ≥2 ng/ml and PSADT ≤10 months) nmCRPC post-primary ADT	Patients with metastatic and patients with nonmetastatic CRPC post-primary ADT
Intervention	N = 933 Xtandi 160 mg/day plus ADT (by either receiving a GnRH agonist/ antagonist or having a history of bilateral orchiectomy)	N = 198 Xtandi 160 mg/day
Comparator	N = 468 Placebo plus ADT (by either receiving a GnRH agonist/antagonist or having a history of bilateral orchiectomy)	N = 198 Bicalutamide 50 mg/day
Primary endpoint	Blinded independent central review (BICR) determined MFS	Investigator-determined progression-free survival (PFS)
Some secondary endpoints	Time to PSA progression, time to first use of antineoplastic therapy, overall survival (OS), QoL (EQ-5D-5L), safety	rPFS, PSA response, time to PSA progression, best overall soft tissue response, time to ≥ 10 point decline of the FACT-P global score, safety

MFS: metastasis-free survival, FACT-P: Functional Assessment of Cancer Therapy-Prostate questionnaire, EQ-5D-5L: European Quality of Life-5 Dimensions-5 Levels health questionnaire

Efficacy endpoints from the PROSPER trial are used in the health economic analysis and the study is considered the most relevant to this assessment since it includes the relevant patient population and relevant comparator. The further description refers only to the trial PROSPER.

Main Study (PROSPER)

PROSPER is a global phase III placebo-controlled study evaluating Xtandi in patients with high-risk nmCRPC. Evidence of metastatic disease was assessed with CT/MRI for soft tissue disease and whole-body radionuclide bone scan for bone disease. Included patients had ECOG performance status of 0 or 1, rising PSA level despite castration-associated testosterone level and PSADT of 10 months or less. The study excluded patients with significant cardiovascular disease. Patients were randomly assigned to a 2:1 ratio, to receive Xtandi or placebo with both arms continuing ADT. Radiographic assessments were performed around every 16 weeks, until confirmation of disease progression (according to RECIST v1.1) or death. The assessments were confirmed by means of central, blinded, independent radiologic review (BICR).

The primary end point was metastasis-free survival (MFS), defined as the time from randomisation to radiographic progression, or as time to death from any cause during the period from randomisation to 112 days after the discontinuation of the trial regimen without evidence of radiographic progression. The primary analysis is based on cut-off date 28 June 2017, after this date the study was unblinded and patients could cross over. As of the data cut-off for the interim analysis 2 (IA2), 31 May 2018, no patients had crossed over from placebo.

Overall survival (OS) was a secondary endpoint in the trial. OS was defined as the time from randomisation to the date of death due to any cause. Three interim analyses and one final analysis for OS were planned. The first pre specified interim analysis for OS was planned at the time of the primary MFS analysis.

Results

The primary endpoint of MFS and all secondary endpoints were analysed using the ITT population, defined as all randomised patients. Overall 68 % in the Xtandi goup and 38 % in the placebo group remained on study drug as of the data cutoff date (28 Jun 2017). The primary reason for discontinuation was disease progression. As of the data cutoff date a total of 219 (23.5%) patients in the enzalutamide group and 228 (48.7%) patients in the placebo group had BICR-assessed MFS events (total of 447 events) see figure 2.

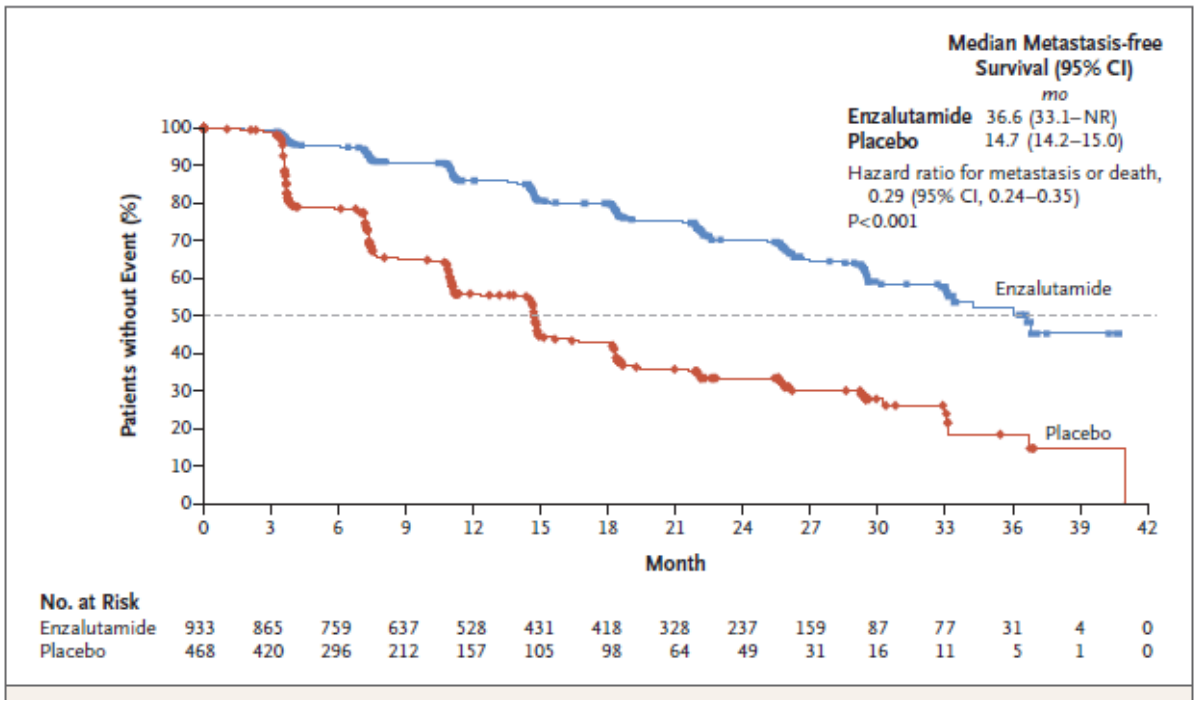


Figure 2: Kaplan-Meier (KM) estimate of metastasis-free survival

The first prespecified interim analysis (IA1) of the endpoints were planned at the time of the final MFS analysis (data cut-off date of 28 Jun 2017), table 3 and figure 3 below. While the analysis of OS did not show a statistically significant decrease in the risk of death, a favorable trend in OS in the enzalutamide group versus the placebo group was observed. The median OS was not reached in either treatment group so the OS data are immature. Median time to follow-up for OS was 23.8 months in the enzalutamide group and 23.0 months in the placebo group.

Table 3: Overview of endpoints (IA1)

End point	Xtandi (N = 933)	Placebo (N = 468)
Metastasis or death – no (%)	219 (23)	228 (49)
Death* – no/total no (%)	32/219 (15)	4/228 (2)
Use of subsequent antineoplastic therapy **Median time to first use – mo** **Patients with use – no (%)**	 39,6 142 (15)	 17,7 226 (48)
Overall survival **Patients who died – no (%)**	 103 (11)	 62 (13)

* *Death was defined as death without evidence of radiographic progression that occurred in the period from randomisation to 112 days after the discontinuation of the trial regime.*

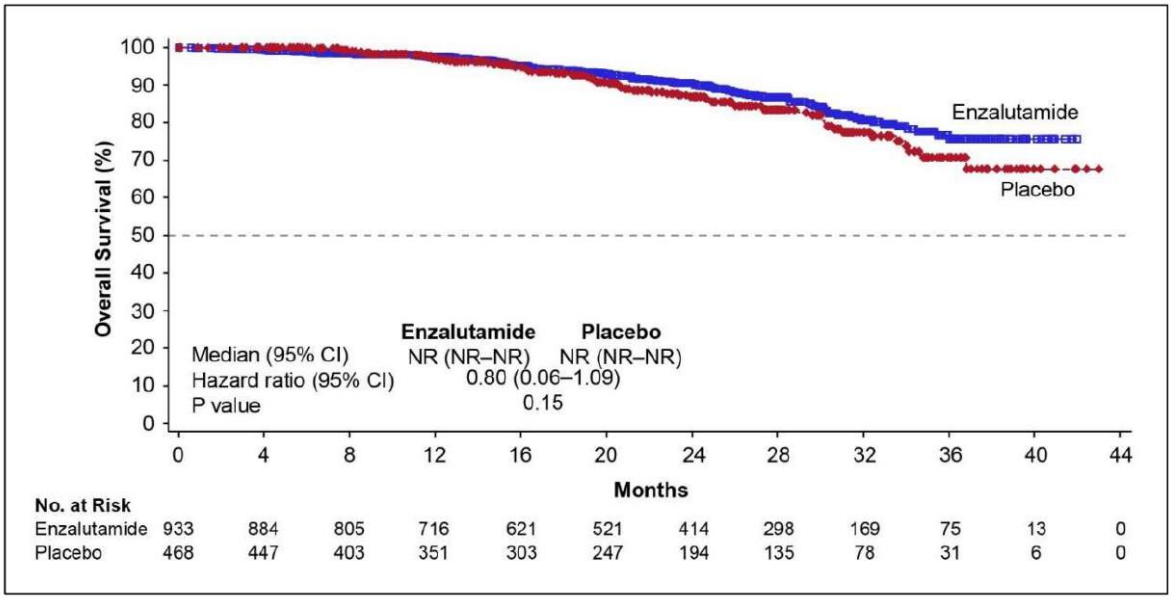


Figure 3: KM curves for OS (IA1)

Xtandi has shown in pre-chemotherapy setting (mildly symptomatic) and in post-chemotherapy stage to increase the life expectancy. In PROSPER the OS data are still immature and second interim analysis (IA2) shows now longer separation of the OS-curves, see figure 4. EMA has stated in EPAR [1] "It remains unknown whether the best use of enzalutamide is in the present line of therapy or rather in later lines, where an OS benefit has been shown." (p. 86) Another concern is the fact that moving forward hormonal therapy could possibly lead to different response (e.g. resistance) to similar hormonal therapy in the metastatic setting.

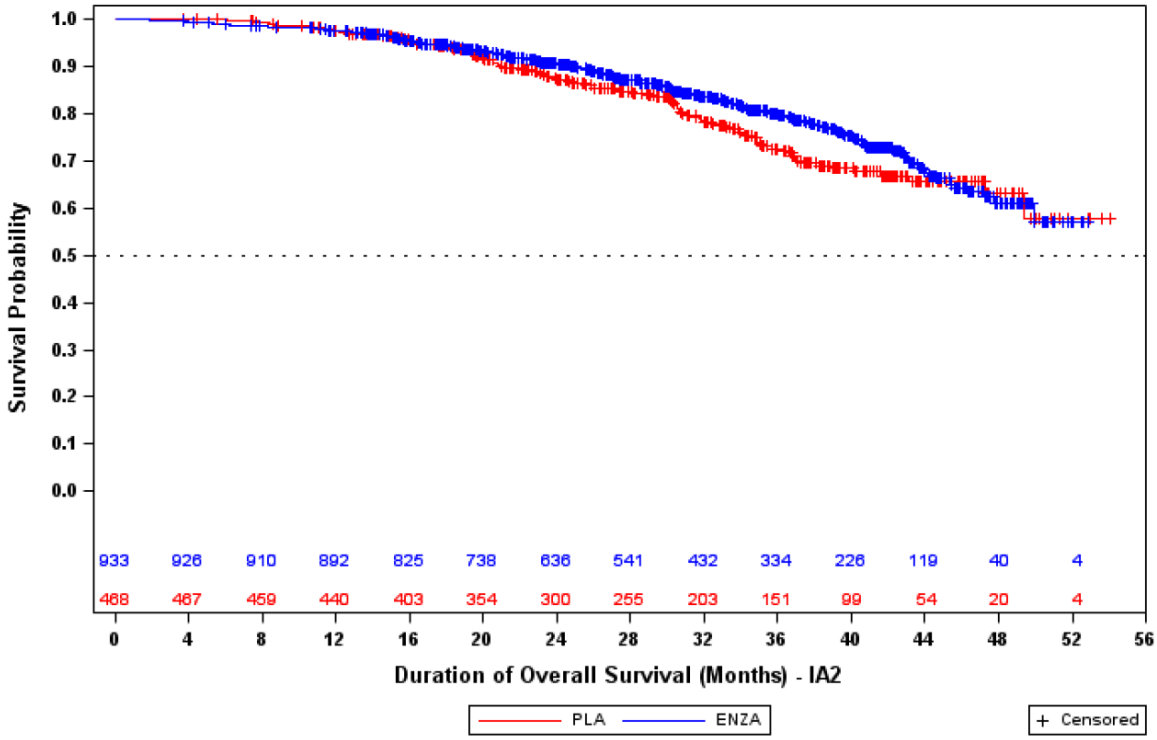


Figure 4: KM curves for OS (IA2)

Patients who progressed while on study drug where allowed to initiate treatment with second line therapy (metastatic therapy). At the time of the first interim analysis 48 % in the placebo

arm were given at least one antineoplastic therapy after treatment discontinuation, compared with 15 % in the Xtandi arm. Table 4 summarize subsequent treatment in PROSPER.

Table 4: Subsequent anticancer therapy

	IA1		IA2	
	Xtandi (n=930)	Placebo (n=465)	Xtandi (n=930)	Placebo (n=465)
Patients taking ≥1 postbasline antineoplastic therapy after treatment discontinuation	244 (26,2)	258 (55,5)	339 (36,5)	310 (66,7)
Zytiga (abiraterone acetate) – no (%)	65 (7,0)	129 (27,7)	101 (10,9)	159 (34,2)
Docetaxel – no (%)	72 (7,7)	94 (20,2)	127 (13,7)	125 (26,9)
Bicalutamide – no (%)	15 (1,6)	29 (6,2)	21 (2,3)	38 (8,2)
Denosumab – no (%)	25 (2,7)	38 (8,2)	41 (4,4)	49 (10,5)
Zoledronic acid – no (%)	21 (2,3)	26 (5,6)	26 (2,8)	34 (7,3)
Leuprorelin – no (%)	49 (5,3)	21 (4,5)	58 (6,2)	25 (5,4)
Antiandrogen – no (%)	20 (2,2)	51 (11,0)	31 (3,3)	82 (17,6)

Safety

The safety profile for Xtandi in the PROSPER trial was consistent with that reported in previous clinical trials involving men with CRPC. The most common adverse reactions reported with use of Xtandi were fatigue, hot flushes, nausea, fractures and hypertension. Other important reactions include fall, cognitive disorder and neutropenia. For patients in the placebo arm most common adverse reactions were fatigue, nausea, diarrhea and hot flushes. Both treatment arms continued ADT treatment, which includes orchiectomy or LHRH analogs. The safety profile for orchiectomy or LHRH analogs are comparable, and mainly related to low testosterone levels. This includes erectile dysfunction, hot flushes, osteoporosis, anemia, loss of muscle mass, fatigue, increased cholesterol levels and depression.

FINOSE discussion

The study stratified patients according to PSADT and previous or current use of bone-targeting agent at baseline, which ensures well-balanced patients population between the two arms. The study included patients with ECOG 0-1, but according to the FINOSE experts Xtandi might be considered in patients with ECOG 2, which could result in poorer OS than estimated from the PROSPER trial. Otherwise, the included patient population in PROSPER reflects the clinically relevant patient population.

In the PROSPER trial they used bone-scans and CT to detect metastases. Both clinical experts and the European guidelines recommend MRI and PET for diagnose of metastasis. With these imaging techniques many patients would be shifted from a non-metastatic state to metastatic state, and hence the patients population would be rather small.

The company has chosen ADT as a comparator. The same comparator is used in the clinical setting, in the pivotal study PROSPER and is the one FINOSE has chosen to be the most relevant comparator. The dosage intensity for Xtandi in PROSPER is in line with recommended dose in the SmPC and is the same used in clinical practice according to the FINOSE experts.

Result from the first interim analysis shows a clear separation of KM-curves for MFS, favoring the Xtandi arm beginning from the first scheduled radiographic assessment (week 17). This is sustained throughout the follow-up period. The assessment of metastasis in the trial was done by BICR which minimizes the bias related to the assessment of metastasis. After the first interim analysis, the study was un-blinded and patients could cross over. None of the patients from the placebo arm crossed over before progression.

Based on IA1, of all patients that had progressed 58 % (129/224) in the placebo arm and 35 % (65/187) in the Xtandi arm received post-progression treatment with Zytiga. The numbers for

docetaxel post-progression are 42 % (94/224) in the placebo arm and 39 % (72/187) in the Xtandi arm. Clinical experts state that Xofigo (radium-233) would be appropriate in the case of isolated skeletal metastases and that most men that entered PROSPER would be fit enough to receive docetaxel after progression on the study drug. From EPAR we can conclude that less than 5 % in either arm received Xofigo post-progression, which does not reflect clinical practice in Sweden and Norway. In clinical practice no patients would receive Zytiga after Xtandi, hence this could affect the OS from the Xtandi arm. Jevtana could also be considered as a post-progression treatment if moving Xtandi further up in the treatment algorithm. The post-progression treatment in the placebo arm does not reflect clinical practice either. Almost all patients should have received treatment with Zytiga and not docetaxel. The impact of subsequent treatment is difficult to estimate since both arms are not in line with what would be used in clinical practice in post-progression setting.

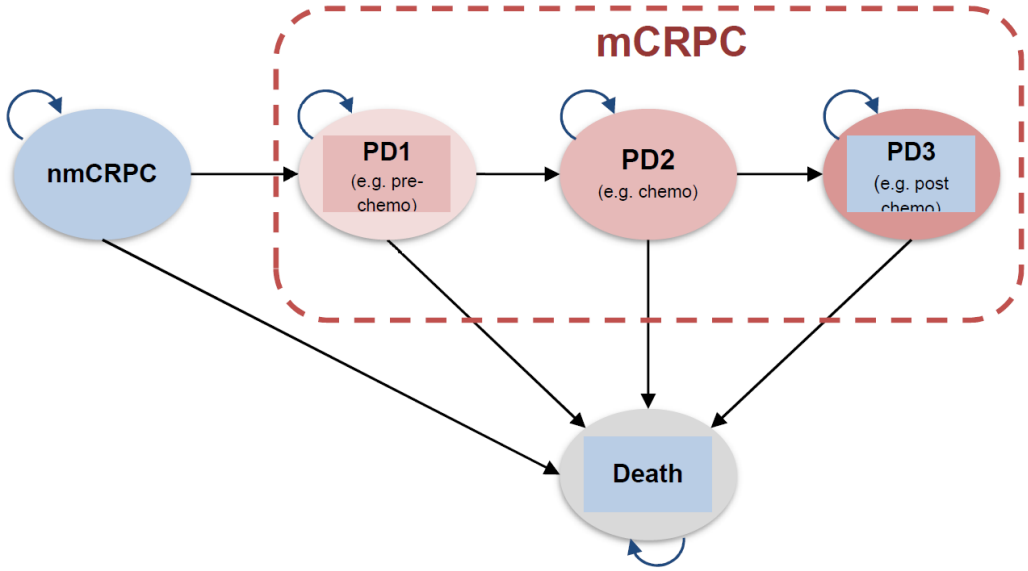
The primary endpoint MFS is a surrogate endpoint for OS. Being able to delay the onset of metastases are of importance, however given that the vast majority of these metastases in prostate cancer are asymptomatic, other endpoints like OS are more important. Delaying the onset of metastasis has not been linked with a considerable increase in OS in the PROSPER trial until now. Due to the immaturity of OS data, the medians are not reached in either group. None of the patients received Xtandi post-progression which makes it difficult to define the right place of Xtandi in a clinical setting, before or after progression.

FINOSE conclusion:
The study PROSPER is considered to have some shortcomings in terms of being able to inform a single technology assessment (STA). The OS data are still immature and it is not possible to assess whether moving forward Xtandi in the treatment algorithm could provide benefit in improving life expectancy. Post-progression treatment given in the PROSPER trial does not reflect what would be given to patients in clinical practice in Sweden and Norway. This again makes it difficult to draw any conclusion about the real effect of Xtandi in non-metastatic setting. However, results from the trial shows a clear separation of the MFS curve.

3 Cost-effectiveness analysis

In order to analyse the cost-effectiveness of treating patients with high-risk, nmCRPC the company compares Xtandi in addition to ADT with ADT alone in terms of cost and health effects.

To fulfill this purpose the company uses a health economic model consisting of three basic phases, non-metastatic (nmCRPC), metastatic (mCRPC) and death. The model is a mix of a partitioned survival analysis and a Markov model. The metastatic phase consists of three different states of progressed disease. Thus, the model altogether consists of five specific states (fig 5).



Abbreviations: nmCRPC: non-metastatic hormone-relapsed prostate cancer; mCRPC: metastatic hormone-relapsed prostate cancer; PD: progressed disease.

Figure 5: Health economic model

Patients are assumed to be 73,5 years old at treatment start. The model has a time horizon which accounts for the life time of the patients.

3.1 Modelling of effectiveness

3.1.1 Clinical effectiveness

The primary endpoint in the PROSPER trial, MFS, informs the model about transitions from nmCRPC to PD1. Due to the limited duration of follow-up in PROSPER, MFS needs to be extrapolated.

According to the company, none of the standard parametric statistical distributions produced an acceptable fit to the MFS Kaplan-Meier in PROSPER. Therefore, more advanced ways of modelling MFS were tested. For the base-case the company chose the flexible spline model with 2 knots and hazard scale.

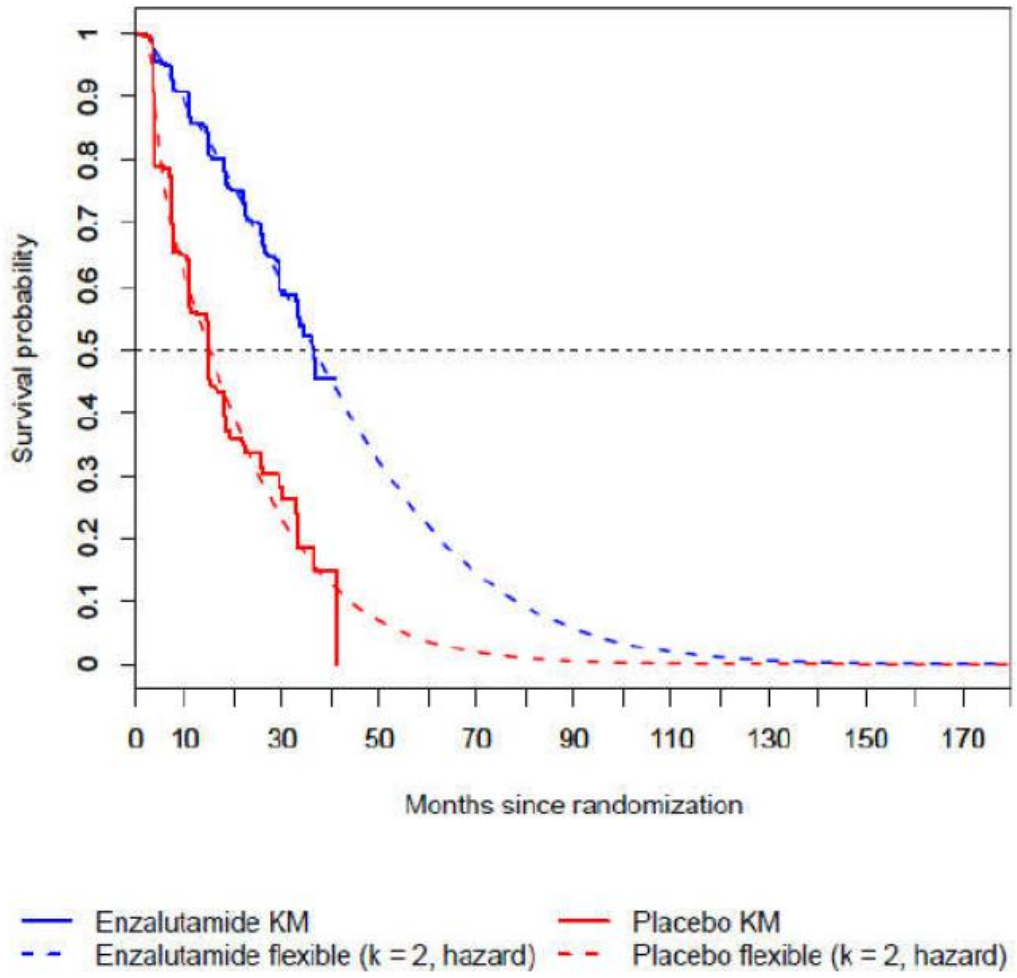


Figure 6: MFS, KM from PROSPER and extrapolation

One clinical study with MFS-data for an ADT-arm with longer follow-up than PROSPER was identified by the company as a validation tool for MFS-extrapolation [13].

Transitions between the PD states were governed by mean treatment durations from studies on Xtandi (PREVAIL, AFFIRM) and docetaxel (TAX 327) in the metastatic phase.

When analysing OS the company chooses to split it into pre-progression survival and post-progression survival. The stated reason for this is the relatively good prognosis of patients in pre-progression disease compared to post-progression. This leads the company to use data from the first interim analysis (IA1) when analysing OS even though OS-data from IA2 is available. According to the company, the splitting of IA2 survival data into pre- and post-progression was hampered due to MFS not being included as an outcome measure in IA2. However, IA2 data did include time to treatment discontinuation (TTD), which is very much correlated with MFS. IA2-data was used in a scenario analysis.

In order to derive the pre-progression survival from the PROSPER data the company performed a time-to-event analysis where death was accounted as an event and patients were censored when they progressed or if they were still alive at the cut-off date. Pre-progression survival was not statistically significantly different between the treatment arms.[1] Weibull was

[1] HR [95% CI] = 0,929 [0,551;1,568]. P-value=0,784

chosen by the company as the statistical distribution with the most plausible fit for pre-progression survival based on visual and statistical criteria.

The company also deemed the Weibull distribution to be suitable for the purpose of extrapolation in post-progression survival. Weibull distribution and log-logistic distribution had the best statistical fit. Validation against external references were made for the comparator arm. PREVAIL was a double-blind, phase 3 study, comparing Xtandi to placebo in asymptomatic or mildly symptomatic mCRPC patients not yet eligible for chemo-therapy. COU-AA-302 was a double-blind, phase 3 study, comparing Zytiga to placebo in a similar patient population. According to the company the Weibull distribution gave the most clinically relevant extrapolation of post-progression survival for the comparator arm based on the PREVAIL Xtandi arm. Based on COU-AA-302 the log-logistic distribution showed the closest match. In the very long run extrapolation with the log-logistic distribution were considered to overestimate OS considering the advanced age and advanced stage of the disease of the patients. Therefore, the Weibull curve was chosen to represent post-progression survival.

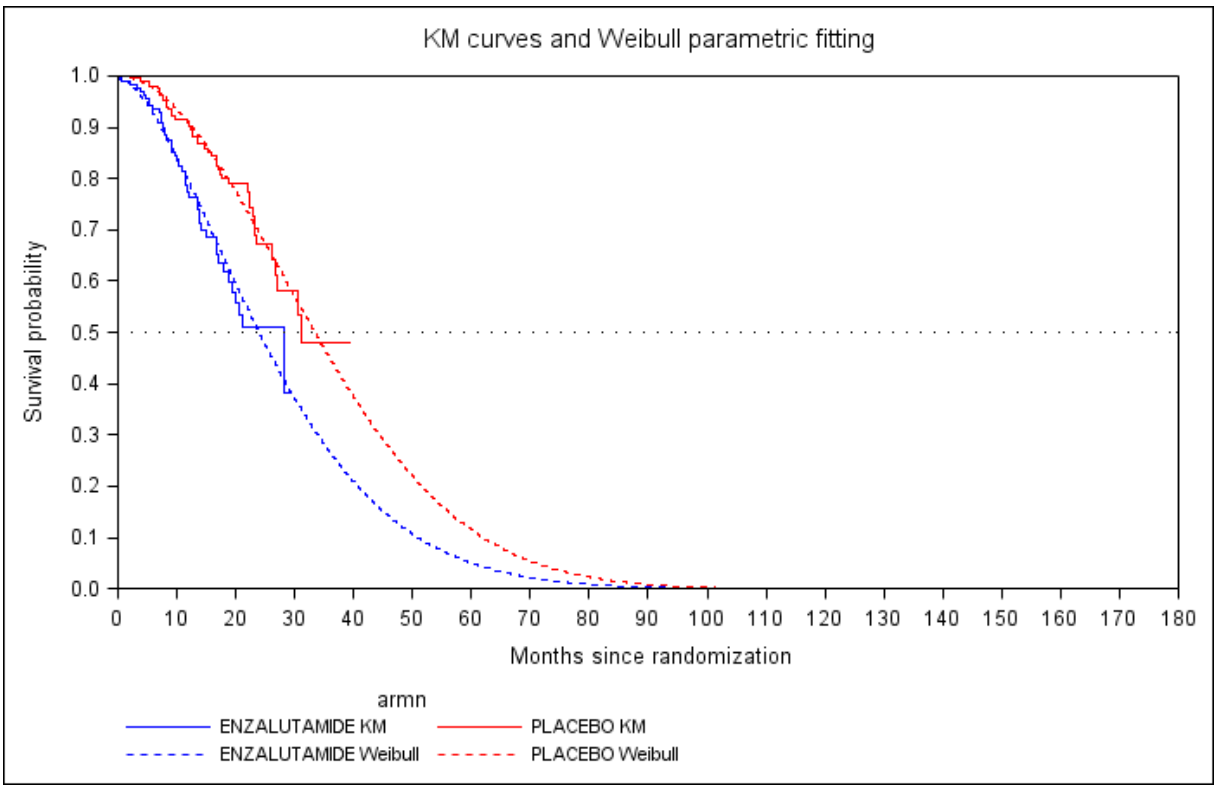


Figure 7: Post-progression survival, KM from PROSPER and extrapolation

Combining the pre- and post progression survival curves leads to the extrapolated OS-curve as in figure 8.

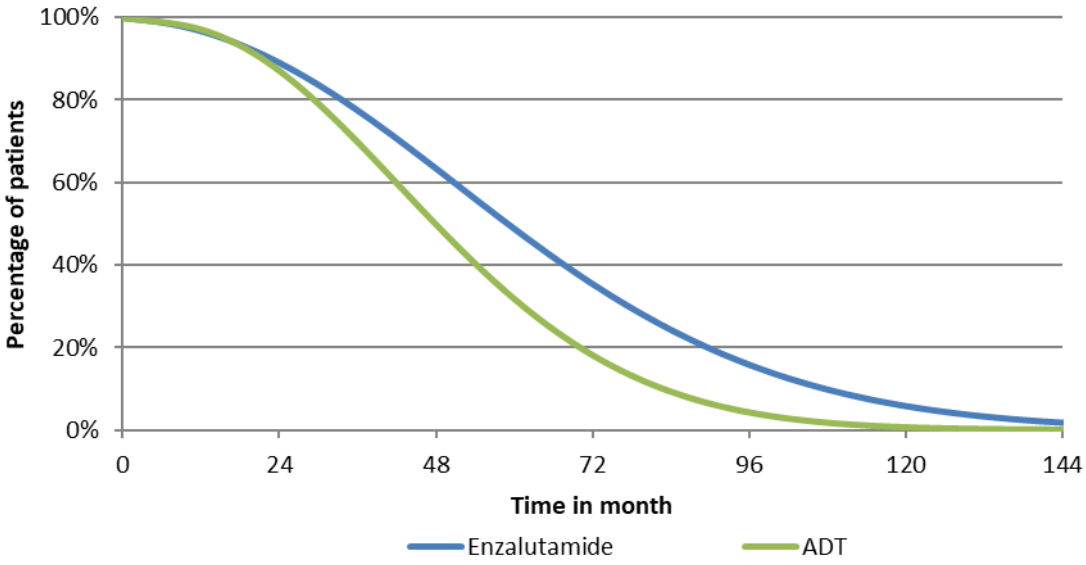


Figure 8: Modelled OS by combining pre- and post progression survival

As a sensitivity analysis the company has done a more traditional partitioned survival model with single modelled OS curves representing the whole time horizon of the patients´ lives. Due to claimed clinical validity the Weibull distribution was chosen to represent OS for both treatment arms in the sensitivity analysis. The company is of the opinion that single OS curves lack face validity because of differing survival rates in pre- and post-progression. Furthermore, they state that there also is too much uncertainty in extrapolating a single OS curve, especially since there is limited external data for validation of the extrapolation. Dividing survival into pre- and post-progression let them use PREVAIL data to validate the extrapolations post-progression.

FINOSE discussion

MFS modelling

Validation of MFS in the ADT arm is done by using TTP (time to treatment progression) in the phase 3 study by Nelson et al. [13]. It is not evident that Nelson et al. supports the validation of MFS. TTP is consistently higher in Nelson et al. than MFS in the ADT arm of both PROSPER and the health economic model, which could be due to method developments in ways of confirming metastases or differences in patient population in the two studies.

MFS of PROSPER is relatively mature when it comes to the ADT arm. That is, however, not the case when it comes to the Xtandi arm why different modes of extrapolation of MFS could have some influence of the results. There is no way of validating the MFS extrapolation of the Xtandi arm.

The company's model has limited choices for sensitivity analyses. This, in combination with the limited possibilities for external data validation of the extrapolation, contributes to large uncertainty in the MFS modelling.

OS modelling

Separating pre-progression survival and post-progression survival is not the standard way of modelling in oncology. The population investigated is a general high-risk population already highly selected for their underlying risk profile. Normally this type of modelling is done when treatments leads to cure, which is not the case in high risk nmCRPC.

A prerequisite of that kind of modelling would be that the curve revealing the sum of the pre- and post-progression survival is in line with the Kaplan-Meier curve. This is in this case questionable. The OS curve of the ADT arm is lower than the Kaplan-Meier curve (IA2) from month 40 and onwards, which is evident when comparing figure 4 and figure 8. Patients at risk in the Kaplan-Meier curve, however, have in that stage decreased to under 100 patients. Still, the difference between the Kaplan-Meier results and the results of the company´s model is large.

When combining pre- and post progression survival in the company´s health economic model OS-curves are separated for a time horizon of more than ten years with a momentaneous hazard ratio that is ever slowly decreasing to the advantage of Xtandi. This is not in line with the EMA conclusion that there is no telling if Xtandi treatment in nmCRPC increases survival compared to Xtandi treatment in mCRPC and not in line with results from PROSPER. The area between the OS curves could thus very well be overestimated.

The company´s main argument for the more than 10 year division of the OS curves is the clinical plausibility of the divergence in MFS transposing into a divergence in OS. Based on 102 completed or ongoing randomised trials Xie et al. [14] reached the conclusion that MFS is a strong surrogate for OS for localised prostate cancer that is associated with a significant risk of death from prostate cancer. FINOSE would, however, want to add that Xie et al only included trials enrolling patients up to 2011. A major treatment shift has since then evolved with the emergence of modern prostate cancer drugs.

As a validation of their pre- and post-progression model the company argues that their post-progression survival modelling of the ADT arm is in line with data from PREVAIL. FINOSE recognizes this but wants to add that there are important differences between the patient populations due to that the patients in this evaluation are selected as a high-risk group. Lower survival would therefore be expected in the post-progression model than in PREVAIL data.

Doubts surrounding the modelled division of the OS-curves are aggravated by the fact that in PROSPER 58 % of the patients in the ADT arm received Zytiga post-progression and none received Xtandi. In the health economic model the company assumes that 100 percent of the patient receive Xtandi post-progression. A larger share of patients in the ADT arm being treated with Zytiga (or Xtandi) post-progression would most probably decrease the area between the OS curves even further.

FINOSE conclusion: FINOSE is of the opinion that the OS modelling made by the company is not appropriate. When considering the evidence there is no room for taking such a large OS effect into account. The extrapolated MFS effect is surrounded with large uncertainty in the company´s model.

3.1.2 Health related quality of life

In PROSPER, health related quality of life was measured with EQ-5D-5L questionnaires at week 1,5,17, and every 16 weeks thereafter during the study period. Week 1 data converted to EQ-5D-3L UK tariff were used by the company in the health economic model for the nmCRPC and PD1 states. The PD2 state health utility was based on the first post-progression value in PREVAIL, where Xtandi was studied in pre-chemotherapy mCRPC. The PD3 health state was based on AFFIRM where Xtandi was studied post-chemotherapy.

Table 5: Utility values used by the company in the health economic model

Utility values		
nmCRPC		0,852
mCRPC	PD1	0,810
	PD2	0,798
	PD3	0,688
End-of-life utility value		0,590
End-of-life duration (months)		3

Besides utility weights connected to different stages skeletal related events and adverse events were incorporated into the model as bringing disutility to the patients. Frequency and disutility of skeletal related events were based upon PREVAIL and the Zytiga study COU-AA-301. Adverse events disutilities and their duration where taken from a number of studies.

FINOSE conclusion: FINOSE has only minor objections concerning the utility weights. Utility probably deteriorates which is not completely adequately handled in the model. The impact of this on the cost-effectiveness results is likely to be minor.

3.2 Utilisation of health care resources

3.2.1 Pharmaceutical drugs

Treatment sequences are assumed to follow the pattern in table 6 in the company base-case scenario. Patients receive Xtandi either in the nmCRPC state or in the PD1 state. In the latter case those deceased in the nmCRPC state are naturally excluded. Otherwise all patients are assumed to receive Xtandi in either of these two states.

Table 6: Assumed treatment sequences

Health state	Xtandi arm	ADT arm
nmCRPC	Xtandi+ADT	ADT
PD1	ADT	Xtandi+ADT
PD2	Docetaxel (40%), ADT (60%)	Docetaxel (40%), ADT (60%)
PD3	BSC	BSC

Treatment duration on Xtandi+ADT and ADT in nmCRPC is in line with time to treatment data from PROSPER. Treatment duration for Xtandi PD1 and PD2 state is as in the PREVAIL [15] and the AFFIRM [16] study where Xtandi was compared to placebo respectively in the metastatic pre-chemo and post-chemo phase. Treatment duration for ADT in PD1 finds it origin from PREVAIL whereas it is considered to be treated equally as long as docetaxel in PD2. Docetaxel TTD stems from the TAX study [17].

3.2.2 Utilisation of health care resources

Assumed visits and testings are made visible in the table below. The assumptions do not differ between the treatment arms.

Table 7: Assumed resource use for care activities used by the company in the economic model

	Frequency per quarter of a year		
	During nm, PD1, PD2 (not docetaxel treatment)	During docetaxel treatment	During PD3
Outpatient visit consultant	1	4,3	0,4
Outpatient visit nurse	3,25	0	0,2*
Community nurse visit	0	0	1,1
CT scan	0,1*	0,1*	1,1
Radiographic/MRI scan	0,1*	0,1*	0,1*
ECG	0	0	0
Ultrasound	0,1*	0,1*	0,1*
Bone scan	0,1*	0,1*	0,1*
Full blood count	1,1	4,3	0,5
Liver function test	1,1	4,3	0,5
Kidney function test	1,1	4,3	0,5
PSA	3,25	4,3	0,5

* The company assumes that only a small proportion of patients receive the care activities in asterisk

3.2.3 Indirect costs

No indirect costs are included in the model.

4 Modelled effectiveness outcome

4.1 Company´s base case scenario

4.1.1 Assumption in company´s base case scenario

The most central assumptions in the company's base case are the following.

- MFS from PROSPER is extrapolated with a flexible spline model.
- Overall survival is partitioned into pre-progression and post-progression survival
- Pre- and post-progression survival from PROSPER were both extrapolated with Weibull distribution.
- Duration of treatment with Xtandi in the non-metastatic phase equals MFS.
- Duration of treatment with Xtandi in the metastatic phase (in the ADT arm) is derived from PREVAIL.

4.1.2 Modelled effectiveness outcome from company´s base-case scenario

Table 8: Company's base case

	Xtandi+ADT	ADT	Difference
Progression-free life years (non-discounted)	3,37	1,62	1,75
Life years (non-discounted)	5,23	4,20	1,03
Quality adjusted life years (QALYs)	3,92	3,17	0,75
Avg treatment duration (months) Xtandi	40,4 (non-metastatic)	20,7 (metastatic)	

4.1.3 Company's scenario analyses

The company has undertaken the following scenario analyses.

Table 9: Company's deterministic sensitivity analyses for both subgroups

Parameters	+/- Life years (non-discounted)	+/- QALYs (discounted)
Base-case	*1,03*	*0,75*
Time to treatment discontinuation (TTD) data instead of MFS data for nmCRPC PD1 transition	0,70	0,50
PROSPER IA2 data instead of IA1 with TTD data instead of MFS	1,15	0,85
MFS piecewise instead of spline survival model	1,51	1,05
No PC mortality in nmCRPC	0,91	0,66
Post progression survival extrapolated with log-logistic distribution instead of Weibull	0,88	0,63
Extrapolated PREVAIL data instead of PROSPER for post-progression survival	1,24	0,86
Single extrapolated OS curve instead of model partitioned in pre- and post progression survival	1,43	0,96
EQ-5D-5L instead of mapping to EQ-5D-3L	1,03	0,77
Chemotherapy in the PD1 (metastatic) state for patients treated with Xtandi in nmCRPC instead of PD2 (i.e. avoiding 7 months delay)	1,03	0,75
No patients opt-out of chemo	1,03	0,75
Incorporating treatment interuptions as in PROSPER	1,03	0,75
Zytiga in PD1 instead of Xtandi for patients initially in ADT arm	1,03	0,72

4.2 FINOSE assessment

For reasons stated above (see FINOSE discussion page 13-14) FINOSE does not agree with the OS assumptions in the model of the company. The main argument of FINOSE is that it can´t be concluded that Xtandi pre-progression leads to an increased long-term survival in comparison with Xtandi post-progression.

The most updated KM (IA2) displayed a small separation of the curves approximately between month 20 and 44. An alternative modelling would therefore be to use KM from IA2 and thereafter assume survival on the same level. A clinical rationale behind it would be that as the patients in the ADT-arm post-metastases receive a more potent treatment than those in the Xtandi-arm the OS curves come together. This modelling would be in line with the KM IA2 and also in line with the conclusion of EMA that it remains unknown whether the best use of enzalutamide is in the present line of therapy or rather in later lines.

However, such a model would only to a limited degree acknowledge increased mortality due to having experienced metastases. Furthermore, it takes consideration of relatively low number of patients at risk at KM convergence (Xtandi 119 and ADT 54, see figure 4). There are, however, no OS data suggesting higher survival in any of the treatment arms at month 44 and beyond.

The company has not technically adjusted the model to make such a scenario possible. It is clear, however, that incremental qalys in this scenario are only a minor fraction of what is assumed in the base-case scenario of the company.

Even in a situation where an assumption of a long-term incremental OS gain is justified, it may not automatically translate into a cost-effective usage of resources, due to the increased costs connected with increased treatment length. Even assuming a long-term OS gain poses problems in the evaluation since the level of the difference is not illuminated.

FINOSE conclusion: Considering the evidence from the PROSPER trial, FINOSE does not find the assumption of a long-term survival gain justified. Without it the larger part of the company´s modelled qaly gain is lost. Since treatment duration and therefore treatment cost with Xtandi in the non-metastatic stage is significantly higher than in the metastatic stage cost-effectiveness in the non-metastatic stage can be hard to conclude, depending on prices in the different countries.

4.2.1 Uncertainty of outcomes

This health economic evaluation is surrounded with a very large amount of uncertainty, which is mainly due to the sparse OS evidence.

5 Assessments in other countries

The CADTH (Canadian) pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) has issued a final recommendation concerning Xtandi in combination with androgen therapy (ADT) for the treatment of patients with nmCRPC. Xtandi is recommended reimbursement on condition that cost-effectiveness is improved to an acceptable level and that feasibility of adoption (budget impact) is being addressed.

National Institute for Health and Care Excellence (NICE) in England has issued an appraisal consultation document on Xtandi nmCRPC. Xtandi in nmCRPC+ADT is compared to ADT alone. Xtandi is preliminary not recommended for treating nmCRPC. This is motivated primarily by cost-effectiveness estimates being uncertain, since evidence whether Xtandi nmCRPC increases survival compared to Xtandi mCRPC is uncertain. Secondly, the estimates are not within the range that NICE usually considers cost-effective.

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