Economic evaluation of mm-398/5-FU/LV for metastatic pancreatic cancer

An explorative cost-effectiveness analysis in a Norwegian setting

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Abstract

Background: Over 700 people develop pancreatic cancer each year in Norway. Approximately 85% of them are diagnosed with metastatic pancreatic cancer. Metastatic pancreatic cancer is the spread of cancer from the pancreas to other organs. The first-line treatment options for these patients are best supportive care and palliative chemotherapy. For second-line treatment, the options are very limited for those who experience progression after chemotherapy, there are currently no other options than best supportive care. A combination therapy of nanoliposomal irinotecan (mm-398), fluorouracil (5-FU) and folinic acid (LV) poses a potential treatment option for the patients that experience progression after receiving gemcitabine based chemotherapy. Another potential treatment is a combination of 5-FU and LV.

Aim: This study is designed to compare the cost-effectiveness of mm-398/5-FU/LV and 5-FU/LV as second-line treatment for metastatic pancreatic patients who experienced progression after being treated with gemcitabine based chemotherapy.

Methods: A Markov model was developed with life years gained (LYG) and costs per LYG as the outcomes. Costs were considered from a health care perspective. The model was both deterministic and probabilistic. A probabilistic sensitivity analysis (PSA) was conducted. The expected value of perfect information (EVPI) was calculated.

Results: The incremental cost of mm-398/5-FU/LV is NOK 998 627; the incremental effect is 2.28 life years gained (LYG). Which gives us an incremental cost-effectiveness ratio (ICER) of NOK 437 247.

Conclusion: MM-398/5-FU/LV is the cost-effective choice if the WTP is NOK 437247 or higher. At a WTP below NOK 437 247, 5-FU/LV is the cost-effective choice. However, more knowledge is needed to minimize the uncertainty in the results.

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List of abbreviations

5-FU	5-fluorouracil
LV	Folinic acid
mm-398	Nanoliposomal irinotecan
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
LYG	Life years gained
WTP	Willingness to pay
ICER	Incremental cost-effectiveness ratio
QALY	Quality adjusted life year
NB	Net benefit
INB	Incremental net benefit
EVPI	Expected value of perfect information
OS	Overall survival
PFS	Progression free survival

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1   Introduction

In Norway around 700 people develop pancreatic cancer each year, in 2014 the number was 736, 360 males and 376 females. The cumulative risk of developing pancreatic cancer by the age of 75 is 0,9 for men and 0,8 for women. The incidence rate for men was 15.3 per 100 000 in 2014, for women it was 13.5. The death rate for pancreatic cancer is very high. One year after diagnosis the relative survival proportion is 24.8% for men and 23.6% for women. After 5 years the number is only 5.5% for men and 6.8% for women. The older you are, the lower the chance of surviving (Cancer in Norway 2014).

The prognosis depends on what stage of the disease the patient is in, and the size of the tumor. There are stages to pancreatic cancer, the patient can have a resectable tumor, a borderline resectable tumor or a non-resectable tumor. Those who have a resectable tumor can undergo surgery to have the tumor removed. Those who have a borderline resectable tumor can go through adjuvant chemotherapy in order to have a surgery later. The patients with a non-resectable tumor cannot undergo surgery (Helsedirektoratet 2015).

Pancreatic cancer does not have many effective treatment options. Today's treatment options for metastatic pancreatic cancer patients in Norway are palliative chemotherapy (gemcitabine) and best supportive care. The best supportive care option consists of several ways of relieving pain. If patients experience obstruction of bile ducts, they can get their bile ducts relieved by endoscopic stents, this is one part of the best supportive care treatment (Helsedirektoratet 2015).

Nanoliposomal irinotecan (mm-398) in combination with fluorouracil (5-FU) and folinic acid (LV) represents a potential treatment option for patients with metastatic pancreatic cancer that progressed after a gemcitabine-based regimen. To my knowledge an economic evaluation of this treatment has not been done before.

However, the results from the phase III trial done by Merrimack pharmaceuticals shows promising results (Wang-Gilliam et al. 2016). My aim with this study is to measure the potential cost-effectiveness of introducing mm-398 in combination with 5-FU and LV as second-line treatment for metastatic pancreatic cancer patients, by comparing it to 5-FU/LV. This study will be done in an explorative context, as there is still very little evidence available for the costs and effects of this treatment.

This paper will consist of seven chapters including this one. The second chapter will be background, where I will provide information on pancreatic cancer and the current treatment options and the new treatment. Chapter 3 will be about the theoretical aspects of economic evaluation, in chapter 4 I will state my research problem and the methods I have used to perform the evaluation. Chapter 5 will consist of the results from my analyses. In chapter 6 I will discuss the strengths and weaknesses of this study. At last I am going to conclude the study in chapter 7.

2   Background

2.1 The pancreas

The pancreas is an organ that is located behind the stomach in the upper left abdomen. Around it are other organs like the liver and spleen. The pancreas is approximately six to ten inches long and it is shaped like a flat pear. The pancreas plays an important role in the conversion of food into fuel for the cells in our bodies. The pancreas has two main functions. The exocrine function helps in digestion, while the endocrine function regulates our blood sugar. The pancreas has three parts, the head, the body and the tail (Columbiasurgery.org).

2.2 Pancreatic cancer

Approximately 2% of call cancer cases in Norway are pancreatic cancer. In most of the cases, the tumor is in the head of the pancreas, in 75% of the cancer cases. A tumor in the head of the pancreas usually grows in to the bile ducts, which can lead to blockage of the ducts. Pancreatic cancer accounts for 5% of all cancer related deaths (Cancer in Norway 2014). The probability of getting pancreatic cancer increases with age, and it is most common around those who are 70 years old. One of the most common symptoms of pancreatic cancer is involuntary weight loss (Nhi.no). A tumor in the pancreas has a lot of space to grow in, so it can take a long time before the patient notices any pain or discomfort. This is why a pancreatic cancer tumor in most cases is not discovered before it has grown and spread. Only 15-20% of those who get diagnosed with pancreatic cancer will have a resectable tumor. This means that at least 80% will have metastatic pancreatic cancer (mPAC) (Nhi.no).

Pancreatic cancer is divided in to 4 stages. Each stage is divided into two categories. Stage 1 is when the cancer is only inside the pancreas and it has not spread, category 1A is when the tumor is smaller than 2 cm, 1B is when the tumor is larger than 2 cm. Stage 2 is divided into 2A and 2B, 2A is when the cancer has spread to

nearby tissues, but has not spread to any large blood vessels or lymph nodes. Stage 2B is when the cancer has spread to nearby tissues and lymph nodes, but no large blood vessels. The pancreatic cancer is in stage 3 if the cancer has grown out of the pancreas and into nearby large blood vessels. Stage 4 is when the cancer has spread to other parts of the body, for example liver or lungs (Cancerresearchuk.org).

In most cases there is no known cause for the development of pancreatic cancer. However, there has been done research that shows that smoking increases the risk of getting pancreatic cancer. There has also been said that obesity and diabetes type 2 has a negative effect when it comes to pancreatic cancer. Having a chronic inflammation in the pancreas will also increase your probability of developing pancreatic cancer (Nhi.no).

If the doctor suspects pancreatic cancer, he has to do some tests in order to determine whether the patient has pancreatic cancer or not, and if yes, how far the cancer has advanced. This can be done by blood tests, imaging diagnostics with CT-scans and transabdominal ultrasound scan (Nhi.no).

The treatment of pancreatic cancer differs between the stages. Those with the least advanced cancer can get the tumor resected with surgery. This treatment is intended to cure the patient. However, like mentioned above, only 15-20% will be eligible for this treatment. For those who have advanced pancreatic cancer there is no treatment intended to cure the patient. These patients will receive palliative treatment. There are some surgeries that can be done with the intent to decrease pain and discomfort for the patient, this could be surgery to drain the bile, or other types of pain relieving surgery. This is all part of the best supportive care treatment for those with metastatic pancreatic cancer. Another option is palliative chemotherapy; this is usually given in the form of gemcitabine. The benefits of palliative treatment are prolonging the patient's life and increasing the quality of life. The median overall survival for those

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receiving gemcitabine is 6.7 months (Helsedirektoratet 2015). However, not all metastatic pancreatic cancer patients can receive this treatment. Hence, some patients will only get best supportive care (Helsedirektoratet 2015). The median overall survival for those who do not get chemotherapy was earlier found to be 2.5 months in USA (Glimelius 1996).

2.3 Current treatment

There are not many options for second line treatment for mPAC, the Norwegian directorate of health suggests FLOX as second line treatment for those who have a response or a stable disease after first line treatment. For those who have a progressive disease after receiving gemcitabine based treatment there is currently no other option than best supportive care (Helsedirektoratet 2015).

2.4 New treatment

The proposed new treatment is a combination of mm-398, 5-FU and LV. All three are invasive treatments. This combination is proposed for the second line treatment of mPAC patients who have experienced progression after gemcitabine based treatment. This treatment is already approved by the U.S Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Merrimack pharmaceuticals is marketing mm-398 under the name Onivyde. LV and 5-FU are already established in the market (Wang-Gilliam 2016). The purpose of mm-398 is to optimize drug delivery and retention in the tumor while also minimizing toxicity.

The phase III trial published by Wang-Gilliam et al. in 2016 shows promising results when it comes to the effects of mm-398/5-FU/LV. The median overall survival for those who were assigned to the combination therapy was 6.1(4.8-8.5), and the progression free survival was 3.1(2.7-4.2). In the 5-FU/LV group the median overall survival was 4.2(3.3-5.3) months, and the median progression free survival was 1.5(1.4-1.8) months. The trial also showed signs of lower toxicity in the mm-398/5-

FU/LV group than in its comparators, which in this trial were 5-FU/LV and mm-398 alone. However, there was higher level of toxicity in the monotherapy group, so mm-398 is not recommended as a monotherapy (onivyde.com).

3 Economic evaluation

According to Drummond et al. economic evaluation in health care can be defined as the comparison of alternative options in terms of their costs and consequences (Drummond et al. 2015). Due to resources being scarce, choices need to be made. In health care the choices are related to for example what pharmaceuticals should be introduced or what type of surgical intervention should be the standard. In order to perform an economic evaluation, you have to compare at least two options with each other, you cannot do an economic evaluation of a treatment without comparing it to some alternative (Briggs et al. 2006). To determine which option is favorable we have to look at all the costs and consequences related to each option. The consequences are the changes in the patients' health, like increased health related quality of life (HRQoL) or quality adjusted life years (QALYs), or life years gained (LYG). The consequences can be either positive or negative (Briggs et al. 2006). The costs refer to the value of tangible resources available, like staff, capital equipment and drugs (Briggs et al. 2006).

Below I will briefly present some background on the methods used for the cost-effectiveness analysis in the thesis.

3.1 Cost effectiveness analysis (CEA)

When we want to compare health care interventions that have different outcomes, we need to assess the costs and consequences of the alternatives (Robinson 1993). Drummond et al. (2015) defined the costs as inputs and the consequences as outputs. In a cost-effectiveness analysis the costs are valued in monetary units, while the consequences are measured in natural units, like for example LYG (Drummond et al. 2015). In my study I will be using LYG as the outcome, so a cost-effectiveness analysis is fitting. In order to compare our alternatives, we need to estimate the incremental costs and incremental LYG. This can be used to get the cost per LYG which will help us determine what the cost-effective decision is. We can also use the

incremental cost and incremental LYG to estimate the incremental cost-effectiveness ratio, which will be explained later in 3.4.1 (Drummond et al. 2015).

3.1.1 Decision analytic modeling

Decision analysis is a systematic approach to decision making under uncertainty. Decision analytic modeling uses mathematical relationships to define possible outcomes of different alternatives. The two most commonly used models in economic evaluation are the decision tree and the Markov model (Briggs et al. 2006).

3.1.2 Decision tree

The decision tree shows the patient's possible prognosis depending on which pathway they take. Each intervention can have a different prognosis (Briggs et al. 2006). In Figure 1, we can see an example of a decision tree. The chance of survival differs between the two pathways, in this particular example, option A has a 20% chance of survival, while option B has 40% chance of survival. The costs can also differ between the options. In Figure 1, the circles are chance nods, and the triangles are the endpoints. The chance nodes each have their branches that could for example be survival and death.

Figure 1: Decision tree, example.
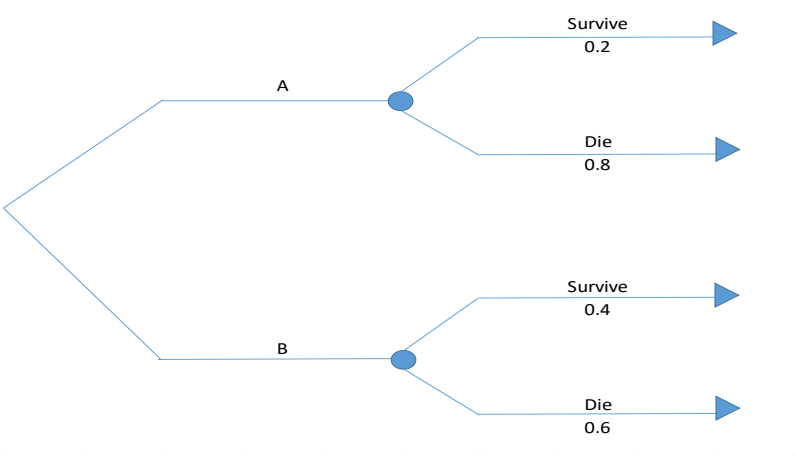
3.1.3 Markov model

The decision tree's main limitation is that it does not take in to account the timing of events. The Markov model is more useful when our decision problem involves continuous risk over time. In a Markov model you can have one event happening several times. A Markov model has a number of states that the patients transition between (Sonneberg et al. 1993). An example of a Markov model is shown in Figure 2, here there are three different states that the patient could be in, well, sick or dead. The arrows show how the patient can move from one state to the other, and also that a patient can stay in a health state. There are no arrows moving from the death state because this is an absorbing state. When we want to compare different treatment strategies, we might have different probabilities for moving from one state to another, so we will need to make a Markov model for each treatment option.

Figure 2: Markov model, example.
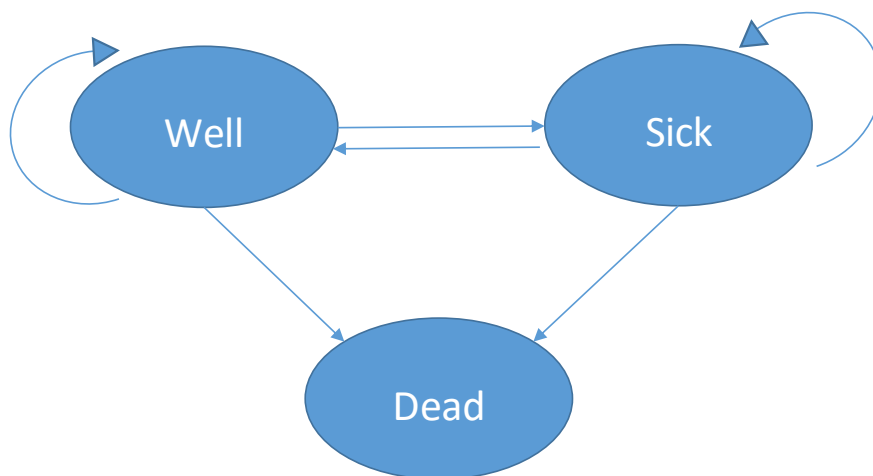
Each arrow has a probability attached to it, that is the probability of moving to a certain state or staying in the same health state. These probabilities are called transition probabilities, they are for a given time interval, like for example two weeks or one month. The intervals are called markov cycles. The transition probabilities can change over time. We can estimate the transition probabilities by using survival analysis. Each health state has both costs and life years attached to it, these are generated during the time spent in the health state. The costs and life years differ

between the health states, for example, those in the sick state probably cost more and generate less life years.

A way to calculate the markov model is through the cohort method. A number of patients is sent through the markov model. The number or proportion of patients that are in each health state is determined by the transition probabilities. For example, if the probability of going from well to sick is 0.40, then 40% of the patients will be in the sick state. An example of a markov cohort is illustrated in Table 1. For simplicity we can assume that the patients cannot move backwards in the model. If we have 1000 patients, then 700 will be in the remission state after the first cycle, 200 will be in the progression state and 100 will be in the death state. The transition probabilities can be applied on each cycle. In Table 2 we can see an example with 5 cycles.

Table 1: Markov cohort, example.

Transition from	Transition to		
	Remission	Progression	Death
Remission	0.7	0.2	0.1
Progression	0	0.4	0.6
Death	0	0	1

Table 2: Markov cohort with 5 cycles.

Cycle	Remission	Progression	Death	Total
0	1000			1000
1	700	200	100	1000
2	490	220	290	1000
3	343	186	471	1000
4	240	143	617	1000
5	168	105	727	1000

3.2 Survival analysis

In order to conduct a survival analysis one has to look at time to event data. The event could be disease progression or death for example. The issue with doing a survival analysis alongside randomized trials, is that the follow-up period is limited. If the event of interest is death, then most likely it will not be experienced by all the participants in the trial. This problem is referred to as censoring. In order to get an accurate estimate for the survival time, it is important to take the censoring in to account. There are several techniques that can deal with this problem, like the Kaplan-Meier product limit method, Weibull and other exponential methods, and also the Cox-proportional hazards method (Prinja et al. 2010).

The most important functions in the Weibull model are the survival function S(t) and the hazard function h(t). The survival is the time to failure, for example death. The hazard is the rate that the event (death) will occur in the next time period, given that is has not occurred yet. The cumulative density function which gives us the cumulative probability of failure (death) up to a certain time is also used in the Weibull model. From these functions we can derive the probability density function for survival, and the cumulative hazard function (Briggs et al. 2006). In Table 3 we can see all these functions.

Table 3: Survival functions.

Function	Formula
Cumulative density	$F(t) = P (T \leq t)$
Survival	$S(t) = P (T > t) = 1 - F(t)$
Probability density for survival	$f(t) = dF (t) / dt = d (1 - S(t)) / dt = - S'(t)$
Hazard rate	$h(t) = f(t) / S(t)$
Cumulative hazard	$H(t) = - \ln (S(t))$

3.2.1 Kaplan-Meier estimator for survival

The Kaplan-Meier method can help us estimate the probability of surviving up to a certain time (t). This is a conditional probability. When using the Kaplan-Meier method we have to estimate the probability that those who survived to the beginning will survive to the end (Bland et al. 1998). For example, the probability that those who are alive at the six months' follow-up will survive for another six months. These survival probabilities are often presented in curves, called Kaplan-Meier curves. The curve is a step function with sudden changes in the probability of survival, corresponding to the times the event was observed (Bland et al. 1998). An example of a Kaplan-Meier curve is illustrated in Figure 3. The short vertical lines indicate censored data (Bland et al. 1998).

Figure 3: Kaplan-Meier curve (Bland et al. 1998).
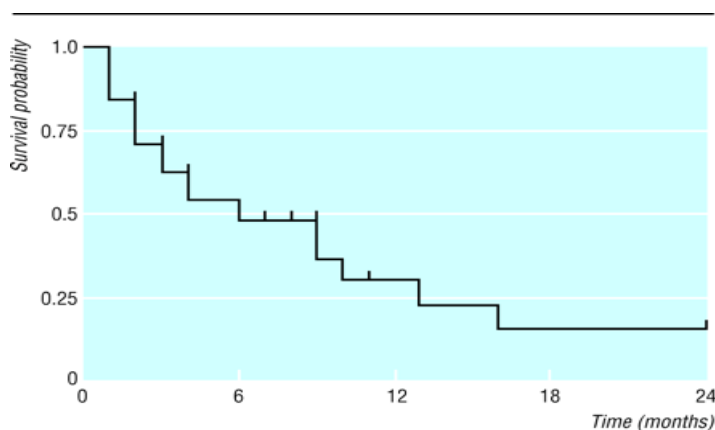
The formula for the Kaplan-Meier estimator is:

$$S(t) = r_1 - d_1/ r_1 * r_2 - d_2 / r_2 * \ldots * r_j - d_j / r_j$$

In this formula, r is the number of people alive at time t and d is the number of people who had experienced the event at time t (Prinja et al. 2010).

The problem with the Kaplan-Meier curves is that they usually have a cutoff point before everyone in the trial has experienced the event (death). In order to estimate

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survival beyond the cutoff point, we can do survival extrapolation, which can be done by fitting a Weibull model to the data (Briggs et al. 2006). Another limitation with these curves is that the sample size decreases by time, so at the far left end of the curve there are only a few people left. This leads to uncertainty. We can see this in the long jumps and flat sections of the curve (Prinja et al. 2010).

The results from clinical studies are often reported in Kaplan-Meier curves. We can use these curves to get the time-dependent transition probabilities that we need for the Markov model. This can be done by fitting a parametric model to the results, a common choice is the Weibull model.

3.2.2 Weibull

The Weibull model has two parameters: the scale parameter (λ) and the shape parameter (γ). The shape parameter (γ) can tell us whether we have a constant hazard, increasing hazard or a diminishing hazard in our model. If γ is 1 it means that the hazard is constant. If it is larger than 1, the hazard is increasing over time. If it is between 0 and 1 it means that the hazard decreases by time (Briggs et al. 2006). If the hazard is not constant, we will need to estimate the transition probabilities for each cycle in our model.

3.2.3 From Kaplan-Meier survival curve to Weibull model to transition probabilities

If we want to make a Markov model, we will need information about the transition probabilities. This information is usually not provided in the articles with the trial results. The transition probabilities could be estimated through individual patient data, but this is usually not provided to the readers due to confidentiality. However, sometimes the articles do feature Kaplan-Meier curves for the overall survival. When individual patient data is not available we can use the Kaplan-Meier curves to estimate the underlying patient data. In addition to the curves, we also need the

number of patients at risk at different time periods, for example every three months (Hoyle et al. 2011). The numbers at risk are sometimes given with the Kaplan-Meier curves in the article. In order to get the data needed, we have to extract the time-to-event data from the Kaplan-Meier curves. After fitting a Weibull model to those data, we will get the estimates for the scale and shape parameters that are used in the Weibull model.

The formula for the transition probabilities is:

$$tp\ (t_u) = 1 - S(t)\ /\ S(t\text{-}u) = 1 - \exp\ (\lambda\ (t\text{-}u)\ -\ \lambda t^{\gamma})$$

So, by using the shape and scale parameters from the Weibull model we can get the transition probabilities we need.

3.3 Uncertainty

3.3.1 Kaplan-Meier

When estimating the Weibull model from Kaplan-Meier survival curves it can be difficult to estimate the uncertainty in a good way, because we do not have the individual patient data. However, a method developed by Hoyle and Henley (Hoyle et al. 2011) does account for the limitations of the Kaplan-Meier curves. This method puts more weight on the model fit to data in the beginning of the trial and less weight on the results in the end of the trial, when there are very few patients left. This could help take the uncertainty into account in a more realistic way than to just fit the Weibull model to the unweighted Kaplan-Meier curve.

3.3.2 Probabilistic sensitivity analysis

It is difficult to say with absolute certainty whether an intervention is going to be cost-effective or not. The issue of uncertainty is not adequately addressed in a cost-effectiveness analysis. In order to get a more robust conclusion in our analysis, we will need to explore the uncertainty in the model and try to account for it (Ghabri et al.

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2016). A way to explore the uncertainty related to the parameters in the model, is to make a probabilistic model. The probabilistic model's objective is to reflect the uncertainty in the input parameters and to describe what this means for the uncertainty over the output. In order to make our model probabilistic, we have to choose a probability distribution that reflects the sampling distribution of the mean for all input parameters (Briggs et al. 2006).

A probabilistic sensitivity analysis (PSA) is a way to deal with parameter uncertainty in a model. The PSA gives an overview of the total effects of the variation in all the uncertain variables. The standard error can tell us how uncertain a parameter is. If the standard error is not available, we can make an assumption as to how big it is, for example, +/- 20%. All variables have a specific distribution. What type distribution, depends on the characteristics of the parameter of interest. For example, the distribution of the cost parameters usually follows a gamma distribution, because the distribution of the costs is often skewed, and the costs do not go below 0. The gamma distribution uses two parameters, alpha (α) and beta (β). By using these parameters, we can obtain expected value and variance (Briggs et al. 2006).

$$\text{Expected value} = \alpha * \beta$$

$$\text{Variance} = \alpha \beta^2$$

If we know the expected value and variance, but not alpha and beta, we can estimate alpha and beta, to model the uncertainty:

$$\alpha = \text{Expected value}^2 / \text{Standard error}^2$$

$$\beta = \text{Standard error}^2 / \text{Expected value}$$

The probability parameters, like the transition probabilities can be assigned a dirichlet distribution, because they have to add up to 1. In the dirichlet distribution alpha is the number of events (r), and beta is 1 – r. After assigning values to α and β, we can make random draws from a gamma distribution.

$$\alpha = r$$

$$\beta = 1\text{-}r$$

The next thing we have to do is a Monte Carlo simulation. This is done by making random draws form the distributions of the parameters. This is done repeatedly, for example, 1 000 or 10 000 times. For each of the draws, we get estimates for incremental costs and incremental effects. We can use these results to make a scatterplot with all the possible combinations of incremental costs and incremental effects. The incremental cost-effectiveness ratio (ICER) can also be obtained from the PSA (Movik 2009).

3.4 Output from the economic evaluation

3.4.1 ICER

The incremental cost-effectiveness ratio tells us about the differences in costs and effects between the treatment options. The formula for finding the ICER is:

$$ICER = C_2 - C_1 / E_2 - E_1 = \Delta C / \Delta E$$

Where C_2 is the cost related to the intervention and E_2 is the effects generated by the intervention. C_1 and E_1 are the costs and effects related to the comparator (other treatment). ΔC is the incremental cost and ΔE is the incremental effect (Briggs et al. 2006).

In order to determine whether an intervention should be implemented or not, we need to know the willingness to pay (WTP). Then we can compare the ICER to the WTP, if the ICER is below the WTP, the intervention should be implemented. The WTP could be expressed in how much we are willing to pay for one life-year gained. This gives us a threshold for the ICER. We can insert the incremental costs and incremental

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effects in a cost-effectiveness plane, where we can see if the intervention should be implemented or not. The cost-effectiveness plane is based on the PSA output (Drummond et al. 2015).

Figure 4: Cost-effectiveness plane, example (Hounton et al. 2012).
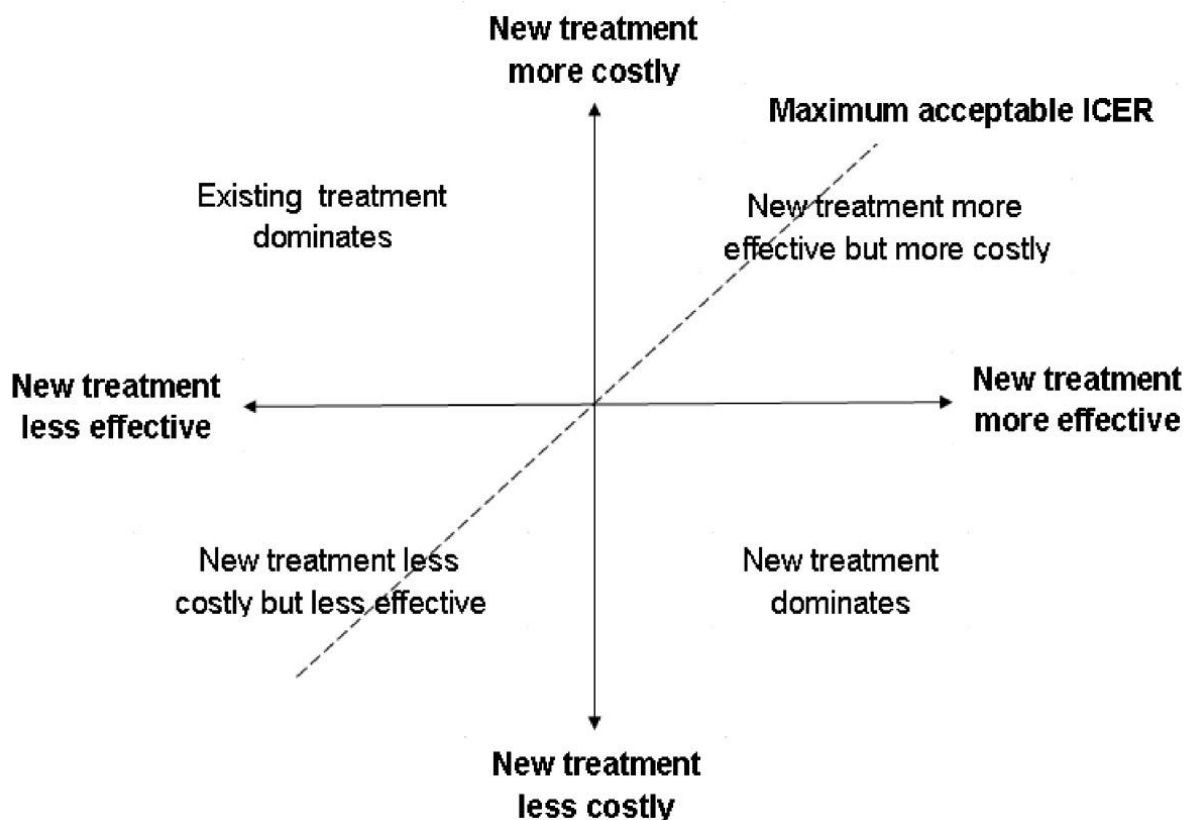
3.4.2 Cost-effectiveness acceptability curve (CEAC)

The CEAC displays the probability of each treatment being cost-effective at different WTP thresholds. In order to make a CEAC we need to calculate the net monetary benefit (NMB). In a probabilistic model, this is done for each of the simulations. The formula for the NMB is:

$$NMB = WTP * (\Delta E - \Delta C)$$

An intervention is considered cost-effective if its NMB is larger than the NMB of the comparator. After estimating the NMB for all our simulations, we can get an estimate for how many times the NMB was larger for the intervention. For example, if we have 1 000 simulations and the intervention has the higher NMB on 500 of the simulations, then the probability of it being cost effective at that WTP is 0.5 (50%). This can then be done with several WTP thresholds (Briggs et al. 2006).

Figure 5: CEAC, example.
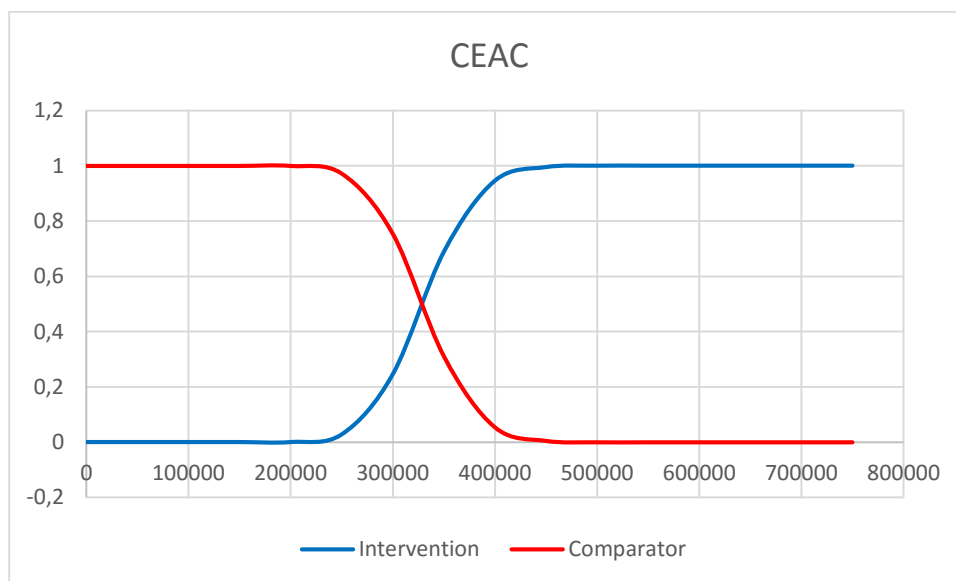
In Figure 5, the y-axis is the probability of a treatment being cost-effective while the x-axis is the WTP. The red line is the comparator, and the blue line is the intervention. As we can see in Figure 5, the different options have different probabilities of being cost-effective at different thresholds. The treatment with the highest probability of cost-effectiveness at our WTP is the one that should be chosen. So, in the example in Figure 5, we should choose the comparator if our WTP is 200 000, but if our WTP is 500 000, we should choose the intervention.

3.4.3 Expected value of perfect information

There is always a chance that the decision we make could be wrong. The cost of making the wrong decision is potential health benefits foregone. The risk of making a wrong decision is linked to the uncertainty in our model. The decision we make based on current information is prone to uncertainty. If we had access to perfect information, we would not make a wrong decision because then there would be no uncertainty. The probability of our decision being wrong is equal to 1 – the value on the CEAC (Briggs et al. 2006). The cost of the uncertainty can be interpreted as the expected value of perfect information (EVPI). In order to get the EVPI, we need to know the net benefit (NB) with current information and the NB in a situation with perfect information (McCullagh et al. 2012).

The formula for the NB is:

$$NB = LYG * WTP - Cost$$

LYG is the number of life years gained by the treatment. We have to calculate the NB for both the comparator and the intervention, so that we can estimate the incremental net benefit (INB). If the INB is larger than 0 than the intervention should be chosen, and if the INB is below 0, the comparator is the cost-effective choice. We need to calculate the INB for all the simulations in our PSA, then we will get an estimate for how often the intervention is the cost-effective choice (McCullagh et al. 2012). For example, if the INB is above 0 on 600 of our 1 000 simulations, it means that there is a 0.6 probability (60%) that the intervention will be cost-effective. We need to calculate the NBs and INB because we need them in the estimation of the EVPI.

The formula for the INB is:

$$INB = NB_{intervention} - NB_{Comparator}$$

We can calculate the NB and INB with several different WTP thresholds and make the CEAC. However, this is all based on current information. The value of the NB could be higher for the comparator in several of our simulations. The expected value of the NB with perfect information is found by choosing the highest NB on all simulations, no matter which treatment it is (Siebert et al. 2013).

The formula for the EVPI is:

$$EVPI = E_\theta max_j NB\ (j,\ \theta) - max j E_\theta NB\ (j,\ \theta)$$

The first part of the formula is the expected value of NB with perfect information, and the second part is the expected value of NB with current information. In this formula j denotes alternatives and θ is a vector of the parameters in the model (Siebert et al. 2013).

Not unlike the CEAC, the EVPI also changes with the WTP threshold. This is due to the fact that the NB is a function of the WTP. The EVPI is also related to the CEAC. The higher the uncertainty, the higher the EVPI is. The point where the uncertainty is at its highest is when it is a 50/50 chance of an intervention being cost-effective. We can plot in both the CEAC and the EVPI in one diagram and see this relationship. As we can see in Figure 6, the EVPI is clearly at its highest where the two CEACs collide. When the probability of one option being cost-effective is close to 1, the EVPI will be close to 0 because it means there is very little uncertainty. If the EVPI is high at our WTP, we need to consider doing further research and gathering more information. If we should invest in additional research or not depends on the cost of that additional information. If the cost is lower than the EVPI, we should invest.

Figure 6: EVPI and CEAC, example.
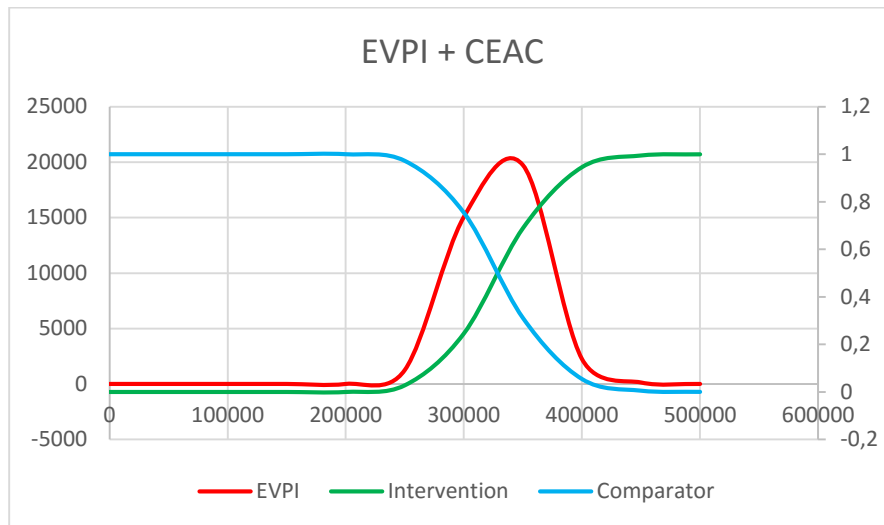
3.5 Transparency and validation

An economic models purpose is to aid decision makers. The decision makers need to know how good the model is at predicting future outcomes, so they can account for it when using the model. There are two ways we can gain the decision makers confidence in our model. Transparency and validation. Transparency is achieved by clearly describing the model structure, equations, parameter values and assumptions, to help the decision maker understand the model. Validity is based on testing our model, for example, by comparing it to other studies or reality (Eddy et al. 2012).

The transparency of a model is divided in two types of documentation, technical and non-technical documentation. The technical documentation includes details about the model, like equations and computer code. The technical documentation should be enough to enable readers with necessary expertise to reproduce the model. The non-technical part refers to descriptions of for example the model and its purpose, sources of funding and their role, and effects of uncertainty. The non-technical documentation gives an overview of what the model does, while the technical documentation enables readers to replicate it (Eddy et al. 2012).

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While the transparency helps readers understand what the model does, and how it does it, it takes validity to know how well it does it. The validity determines if the model is going to be useful for decision makers. There are five types of validity: face validity, internal validity, cross-validity, external validity and predictive validity. Face validity is how well a model corresponds to current science and evidence, this is judged by experts on the field. Internal validity checks if the model behaves as it should and if it is implemented correctly. Cross-validity is achieved by comparing the results of the model with other models in the field. External validity is using the model to simulate a real scenario, like a clinical trial and comparing the simulated results with the trial results. Predictive validity is achieved by comparing the models predictions with what really happened, this is a done a while after the study, to see how well the model predicted real life events (Eddy et al. 2012).

3.6 Literature review on economic evaluation of mm-398/5-FU/LV treatment for pancreatic cancer patients

To my knowledge there has not earlier been done an economic evaluation of mm-398/5-FU/LV in the treatment of progressed metastatic pancreatic cancer patients. The databases used to search for mPAC data, economic evaluations, and overall survival (OS) were, Google Scholar and PubMed. For OS the searches were focused on clinical trials for the relevant treatment strategies. For the costs, I used data from the Norwegian Medicines Agency and published articles of economic evaluations.

4   Research question, materials and the model

4.1 Research question

The aim of this study is to determine if mm-398/5-FU/LV is a cost-effective treatment compared to 5-FU/LV, for metastatic pancreatic cancer patients who experienced progression after receiving gemcitabine based treatment. The intervention is compared to 5-FU/LV. The results will be based on a survival analysis and a Markov model. The uncertainty will be explored with PSA and EVPI.

4.2 Material

For the effects of the treatment alternatives, I used the article written by Wang-Gilliam et al. in 2016, based on the clinical trial for mm-398/5-FU/LV. This study provided the median overall survival (OS) and median progression free survival (PFS). I also got the Kaplan-Meier curves from the same article. For the probabilities of responding to the treatment or progressing or dying, I used Merrimack's own webpage for mm-398, called onivyde.com.

Table 4: Median OS, median PFS, response rate, progression rate and death rate.

Variable	5-FU/LV	mm-398/5-FU/LV
OS (95% CI)	4.2 (3.3 – 5-3)	6.1 (4.8 – 8.5)
PFS (95% CI)	1.5 (1.4 – 1.8)	3.1 (2.7 – 4.2)
Response	0.008	0.08
Progression	0.27	0.26
Death	0.72	0.66

For the drug costs, I used the Norwegian medicines agency's webpage. For the nursing costs, I used a report published by Spekter employers' association. This report provided the hourly wage for specialist nurses, including payroll taxes. The transportation costs were provided by Aaserud et al. in an article written in 2007. The preparation costs were taken from an article written by Norum et al. in 2007. The cost of stay was also provided by Aaserud et al. (2007). I got the cost of mm-398 from Onivyde.com, the price is 1 620 dollars. However, this was the price in the U.S market, so the potential price of mm-398 in Norway may be higher.

Table 5: Cost components, costs in NOK.

Component	Unit cost	5-FU/LV (per cycle)	mm-398/5-FU/LV (per cycle)
mm-398	13 446	-	40 338
5-FU	337.3	337.3	337.3
LV	4 154	1 662	2 077
Nurse	378.48	9 272.52	18 167
Transportation	410	820	820
Preparation	234	468	702
Cost of stay	822	822	1644

The total nursing costs are based on infusion time, provided my Merrimack pharmaceuticals own webpage, onyvide.com. The infusion time for each treatment is presented in Table 6. The total preparation cost is based on the number of drugs, in the comparator group, only 5-FU and LV have to be prepared, while in the intervention group, mm-398 also needs preparation.

Table 6: Infusion time.

Drug	Comparator	Intervention
5-FU	24 hours	46 hours
LV	30 minutes	30 minutes
mm-398	-	90 minutes

The total drug costs are based on the recommended dosage of each treatment. This information was provided in Onivyde.com. The recommended dosage of the intervention is 70 mg/m^2 of mm-398, 400 mg/m^2 of LV and 2400 mg/m^2 of 5-FU. The dosage used in the comparator group was, 200 mg/m^2 of LV and 2000 mg/m^2. In this study, the total drug costs are based on a person that weighs 70 kg and is 175 cm tall. Which makes the body surface 1.84m^2.

Table 7: Drug dosage and costs in NOK.

Drug	Packing	mg per ml	Used for	Dose per cycle	Cost per cycle
Fluorouracil Accord	1x100 ml	50	Comparator	368 mg	337.3
	1x100 ml	50	Intervention	736 mg	337.3
Kalsiumfolinat Pfizer	10x10 ml	10	Comparator	3680 mg	1 662
	10x10 ml	10	Intervention	4416 mg	2 077
Onivyde (mm-398)	1x10 ml	4.3	Intervention	128.8 mg	40 338

For the effects of gemcitabine, which was the first-line treatment, I used an article written by Von Hoff et al. in 2013 and another article which was written by Conroy et al. in 2011. For the costs I used the Norwegian Medicines' Agency webpage, Spekter.no and an article written by Vogler et al. 2016. The costs and effects of Gemcitabine are presented in Appendix V. In Table 8 are all sources for costs and effects listed.

Table 8: Source material used in the economic evaluation

Source	Used for	Treatment
Wang-Gilliam et al. 2016	OS and PFS	mm-398/5-FU/LV and 5-FU/LV
Onivyde.com	Response, progression, death Price of mm-398	mm-398/5-FU/LV and 5-FU/LV
Von Hoff et al. 2013	OS and PFS	Gemcitabine
Conroy et al. 2011	Response, progression, death	Gemcitabine
Legemiddelverket.no	Drug costs	5-FU and LV
Spekter.no	Nursing costs	mm-398/5-FU/LV and 5-FU/LV and Gemcitabine
Aaserud et al. 2007	Transportation costs and cost of stay	mm-398/5-FU/LV and 5-FU/LV and Gemcitabine
Norum et al. 2007	preparation costs	mm-398/5-FU/LV and 5-FU/LV and Gemcitabine
Vogler et al. 2016	Drug cost	Gemcitabine

4.3 The model

This study is based on a randomized controlled trial in which 417 patients from 14 countries were enrolled. There were 3 different groups in the trial, the mm-398/5-FU/LV treatment group, the 5-FU/LV group and a mm-398 monotherapy group. The trial period went from 2011 until 2014 (Wang-Gilliam et al. 2016).

The study population was mPAC patients who were 18 years or older and had experienced progression after receiving gemcitabine based treatment (Wang-Gilliam et al. 2016).

In my model I will only compare mm-398/5-FU/LV and 5-FU/LV. This is because Wang-Gilliam et al. stated in 2016 that there was no significant difference in the outcomes of 5-FU/LV and mm-398 monotherapy. Hence, the Markov model has two strategies. Both strategies include both first-line and second-line treatment.

Table 9: Treatment strategies in my Markov model.

	Comparator	Intervention
First-line	Gemcitabine	Gemcitabine
Second-line	5-FU/LV	mm-398/5-FU/LV
Cycle-length	1 week	2 weeks

The cycle lengths are different since those in the strategy 1 group receive treatment once every week, while those in the second strategy only receive treatment once every two weeks. However, the models for both treatments go over 450 days. In my model there are two health states, alive and dead. The transition probabilities are time dependent and based on the Kaplan-Meier curve for OS that was published alongside the trial. In Figure 7 we can see an illustration of the Markov model. The decision tree used in the model is presented in Figure 8.
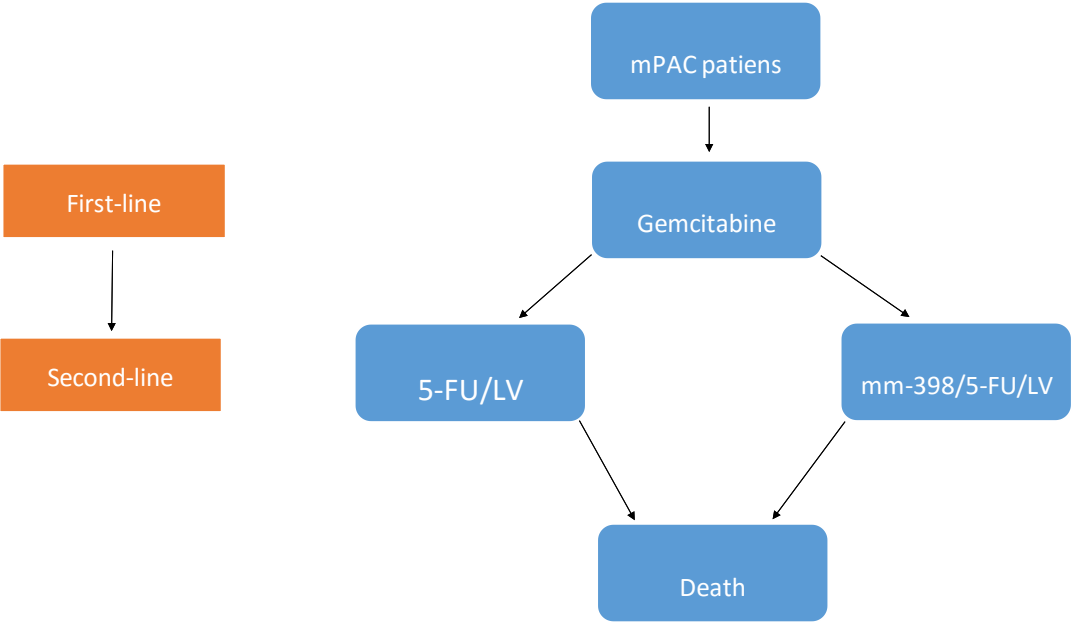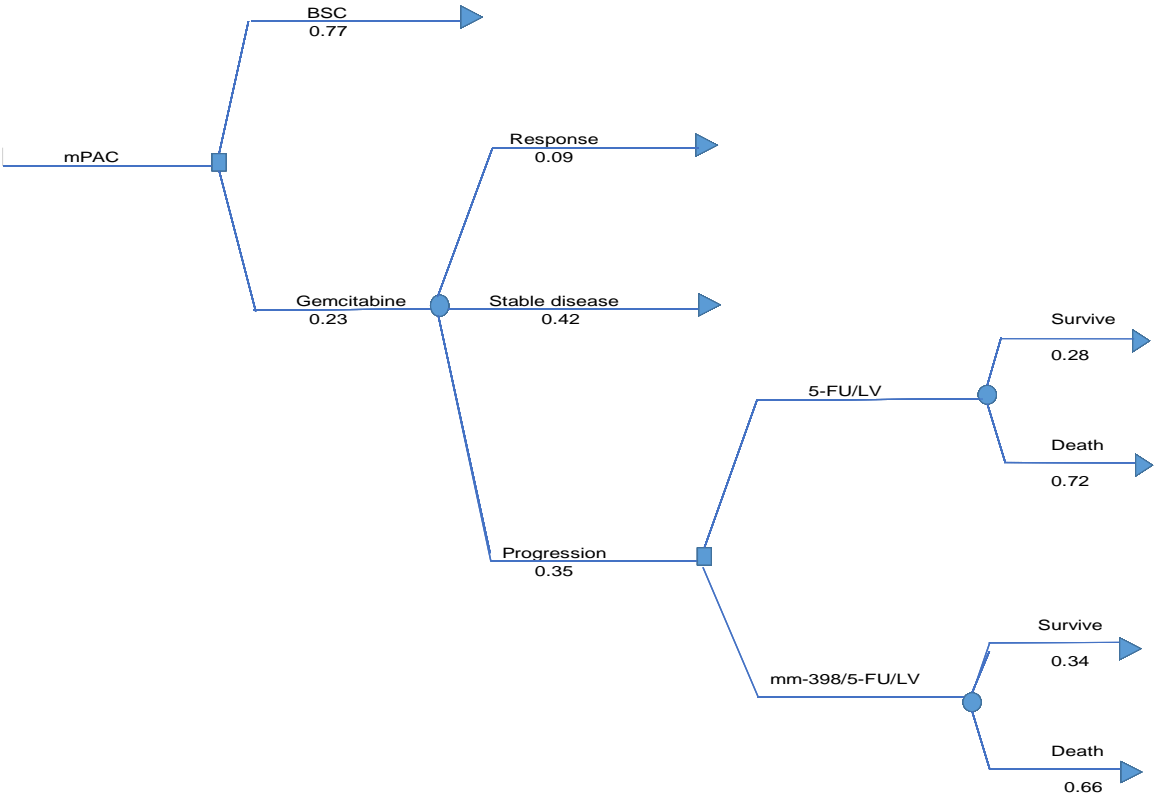
Figure 7: The Markov model

Figure 8: Decision tree

4.3.1 Estimation of the time dependent transition probabilities

I used a plot digitizer program to extract the probabilities for survival from the published Kaplan-Meier curves for the intervention and the comparator. The Kaplan-Meier curves from the article are displayed in Appendix I. The probabilities were inserted in the Excel spreadsheet published by Hoyle and Henley in 2013, along with the numbers of patients at risk every three months. The time intervals in the spreadsheet were three months divided by 4 because the spreadsheet was set up in that way. Hence, the probabilities for survival were plotted in for every 22 days. A picture of the spreadsheet can be found in Appendix II. After plotting in all the available numbers, I used the statistical package R to fit a Weibull model to the survival data. This gave me the parameters I needed to estimate the transition probabilities. I used two separate sheets to fit the Weibull model, one for the intervention and one for the comparator. The fitted Weibull curves can be seen in Appendix III and Appendix IV.

Table 10: Weibull parameters used for transition probabilities.

	mm-398/5-FU/LV	5-FU/LV
λ	0.00017468	0.00120506
γ	1.5542607	1.27634433

From the formula given in 3.2.3, the transition probabilities for the intervention were estimated by:

$$tp\,(t_u) = 1 - exp\,(0.00017468\,(t\text{-}u) - 0.00017468\,t^{1.5542607})$$

And for the comparator by:

$$tp\,(t_u) = 1 - exp\,(0.00120506\,(t\text{-}u) - 0.00120506\,t^{1.27634433})$$

The transition probabilities were assigned a dirichlet distribution for the probabilistic sensitivity analysis.

4.3.2 Health outcome

I decided to use life years gained as the health outcome in my model. This was calculated through the Markov model. I estimated the proportion of people still alive at the end of each cycle and summed them up at the end (after 450 days). This was done separately for each treatment alternative. I calculated the probability of staying alive each cycle by taking 1 minus the transition probability to death in each cycle.

4.3.3 Costs

This study is done from a health care provider's perspective. Hence, the costs included in the analysis are those incurred by the health service. The costs included are drug costs, nursing costs, preparation costs, transportation costs and cost of stay. All costs are calculated in Norwegian krone (NOK). For the costs that were only available in U.S dollars ($) I used a conversion rate of 1 $ = 8.3 NOK. For the costs provided in Euros, I used a conversion rate of 1 Euro = 9.5 NOK. All future costs were discounted at a rate of 4 %. Costs from previous years were adjusted for inflation with ssb's inflation calculator.

All the costs were assumed to follow a gamma distribution. The standard error of the cost estimates was not available in the literature, so I assumed an uncertainty of 20%. The standard error was based on the formula of a 95 % confidence interval.

$$95\% \text{ CI} = \text{Expected Value} \pm 2 - \text{Standard Error}$$

$$-2*\text{Standard Error} = 0.8*\text{Expected Value} - \text{Expected Value}$$
$$-2*\text{Standard Error} = -0.2*\text{Expected Value}$$
$$\text{Standard Error} = 0.1*\text{Expected Value}$$

4.3.4 Cost-effectiveness analysis

In this study the cost-effectiveness of the intervention is based on the incremental cost-effectiveness ratio (ICER). The ICER is then compared to maximum willingness to pay thresholds.

4.3.5 Statistical analysis

I did most of my statistical analyses in Microsoft Excel 2016. The decision tree and the Markov model were made in Excel. I performed the probabilistic sensitivity analysis in Excel as well. The PSA had 1 000 simulations of costs and effects generated by the comparator and the intervention. The simulations were used to estimate the ICER, INB and the EVPI. From the PSA, I created a CEAC and a cost-effectiveness plane. The cost-effectiveness plane and CEAC were constructed in Excel. The confidence intervals for the costs and effects were estimated in STATA.

For my survival analysis, I used several software programmes. First, I used a plot digitizing program called Get data graph digitizer, then I used the Excel sheet from Hoyle and Henley. I used statistical package R to fit a Weibull model to my data.

5   Results

5.1 Costs and effects

The expected cost per patient in the 5-FU/LV group is NOK 303 154. In the mm-398/5-FU/LV group, the expected cost is NOK 1 301 782. The expected effect in the 5-FU/LV group is 8.15 LYG. In the mm-398/5-FU/LV group, the expected effect is 10.43 LYG. This gives us an incremental cost of NOK 998 627 and an incremental effect of 2.28 LYG. The incremental cost-effectiveness ratio amounts to NOK 437247. The cost per LYG was NOK 124 787 for mm-398/5-FU/LV and NOK 37 205 for 5-FU/LV.

Table 11: Deterministic results

Treatment	Cost	LYG	ICER	Cost per LYG
5-FU/LV	303 154	8.15	-	37 205
mm-398/5-FU/LV	1 301 782	10.43	437 247	124 787

Table 12: Probabilistic results

Treatment	Mean costs (95% CI)	Mean LYG (95% CI)
5-FU/LV	304 143 (302 819 – 305 467)	8.17 (8.16 - 8.18)
mm-398/5-FU/LV	1 332 346 (1 326 407 – 1 338 285)	10.46 (10.45 - 10.47)
Mean difference	1 028 203 (1 022 119 – 1 034 287)	2.29 (2.27 - 2.30)

The results from the probabilistic sensitivity analysis are listed in Table 8. The mean values are the means of all the 1 000 simulations in the PSA. The probabilistic results are not that different from the deterministic results.

From the cost-effectiveness plane in Figure 8, we can see that all the simulated results from the PSA are on the same side in the cost-effectiveness plane. All the simulations had higher costs and more life-years gained. The red line signifies a maximum WTP of NOK 450 000. The points under the line are cost-effective, while those over the line are not cost-effective.

Figure 9: Cost-effectiveness plane.
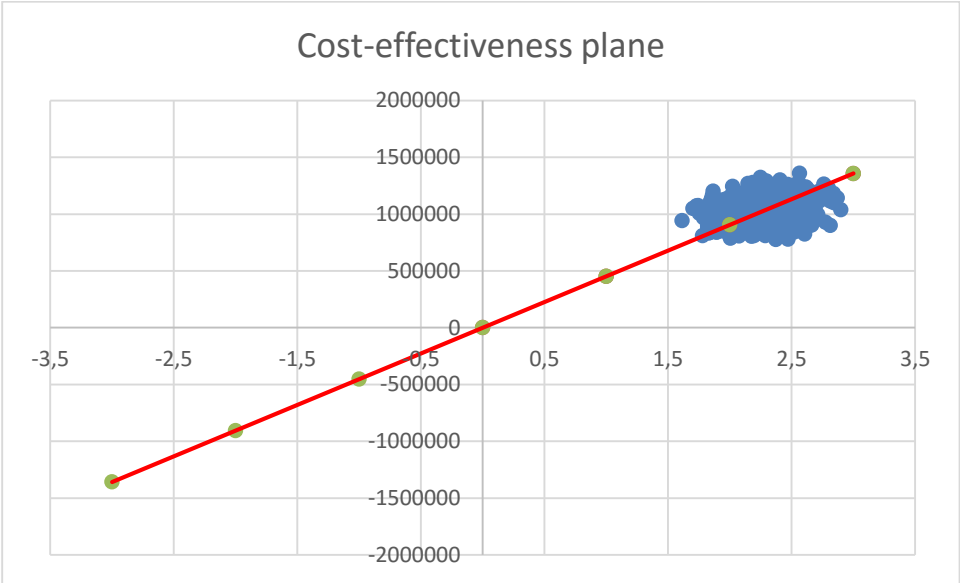
The CEACs for both treatment options are presented in Figure 9. We can see that the intervention has the highest probability of being cost-effective as long as our willingness to pay is above NOK 450 000. If the WTP is less than NOK 450 000 we should choose the comparator. If it is above NOK 450 000 we should choose the intervention.

Figure 10: CEACs for comparator and intervention
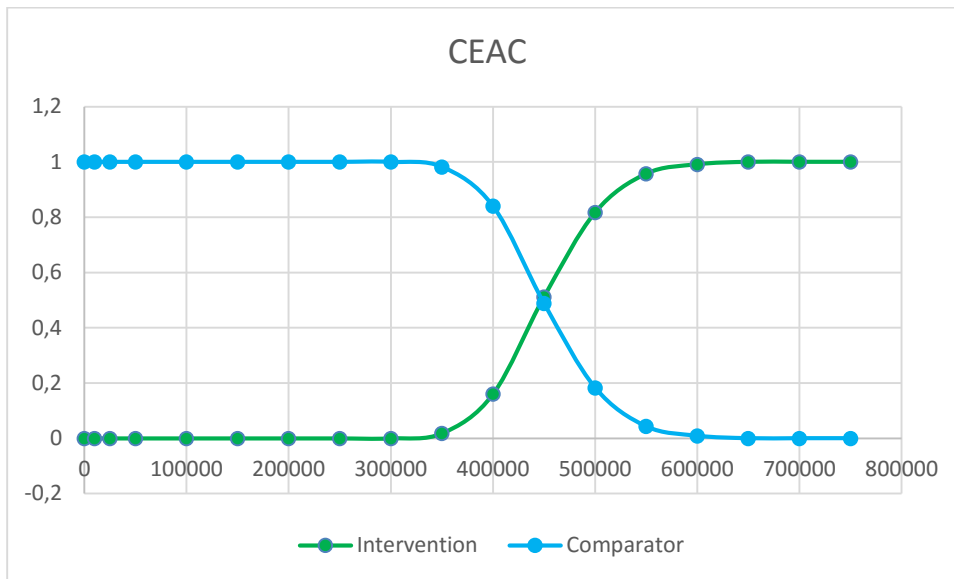
From the CEAC we see that the intervention has a 16% probability of being cost-effective at a WTP threshold of NOK 400 000. If the threshold is 450 000 NOK, the probability of cost-effectiveness increases to 48.8%. At a threshold of NOK 500 000, the probability of the intervention being cost-effective is 81.7%.

The expected value of perfect information is at the highest when the WTP is between NOK 450 000. This corresponds well with the CEACs in Figure 9. When the comparator and the intervention have the same probability of cost-effectiveness, the uncertainty is at its highest. Hence the EVPI is the highest at the same point. The EVPI is illustrated in Figure 10. At a WTP of NOK 450 000, the EVPI is NOK 48 439.

Figure 11: EVPI
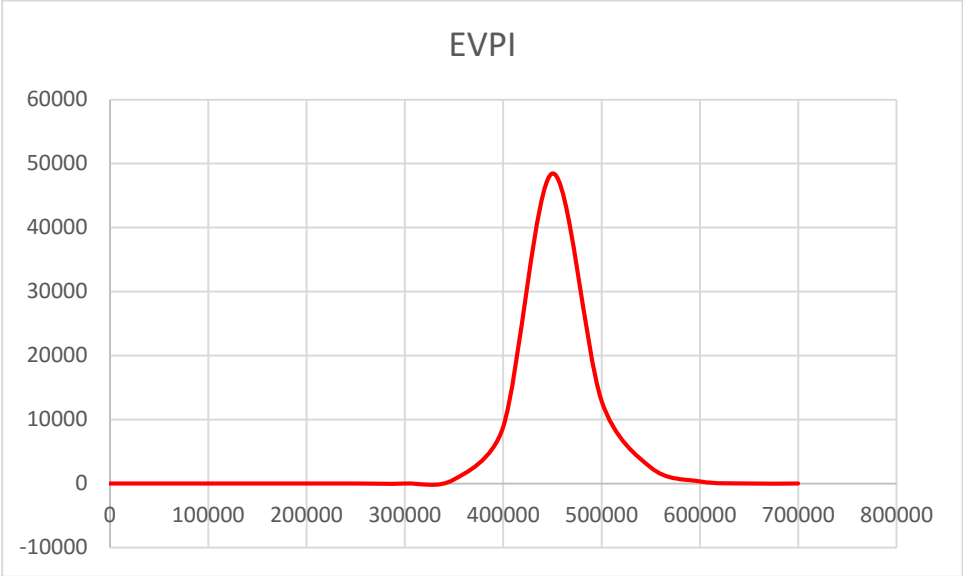
6   Discussion

6.1 Main findings

In this cost-effectiveness study, the intervention had higher costs and more life years gained than its comparator. The estimated cost per LYG was NOK 37 205 for 5-FU/LV, and NOK 124 787 for mm-398/5-FU/LV. The estimated LYG was 8.15 for 5-FU/LV and 10.43 for mm-398/5-FU/LV. The estimated cost per patient was NOK 303 154 for 5-FU/LV and NOK 1 301 782 for mm-398/5-FU/LV. The higher costs could be explained by the longer infusion time of 5-FU which leads to higher nursing costs and the addition of cost of stay. The cost of mm-398 also has a great impact on the total costs in the intervention group. The intervention has a higher probability of being cost-effective at all WTP thresholds above NOK 437 247.

6.2 Strengths and weaknesses

6.2.1 The study

This study is based on limited evidence. However, it is the first health economic study of mm-398/5-FU/LV for mPAC who experienced progression after receiving gemcitabine based treatment.

6.2.2 Probabilities

A big weakness in this study is the sources used to derive the probabilities that are used in the model. I did not have access to individual patient data, so all probabilities are based on abstracted data. The transition probabilities in the model are based on Kaplan-Meier curves. The problem with Kaplan-Meier curves is very few observations over time. After 12 months, only 8 patients were at risk in the intervention group (Wang-Gilliam et al. 2016). This could lead to overfitting of the empirical data (Diaby et al. 2014). In order to reduce this problem, a Weibull distribution was fitted to the data from the Kaplan-Meier curves. However, the Weibull curves were based on limited data. There was no available information about

censoring in the trial. However, the Hoyle and Henley method does account for that in the model.

6.2.3 Life years gained

The health outcome in this study is life years gained. This is a relatively transparent method for measuring population health. However, it does not take in to account pain and the patients physical ability (Robberstad 2005). The LYG method values a year in perfect health and a year in pain exactly the same way. The clinical trial showed higher occurrence of adverse events in the mm-398/5-FU/LV group than in the 5-FU/LV group (Onivyde.com). Hence, further research may be needed to assess the differences in quality adjusted life years (QALYs). In Norway the maximum WTP for a QALY is considered to be NOK 500 000 (Government.no: NOU 2012:16). In this study the ICER is just under NOK 500 000 for a life year. However, this is for a life year that might not be in perfect health. The patients who go through palliative care are most likely not in perfect health. Hence, the maximum WTP for a LYG may not be NOK 500 000. This could have an effect on whether we consider the intervention cost-effective or not.

6.2.4 Health states in the Markov model

The Markov model only includes two health states, survival and death. This was done due to limited available data. It was also done to simplify the model and make the outcome (LYG) clear. However, there may be other important events happening, like for example disease progression.

6.2.5 Costs

One of the strengths of this study is that, most of the costs are taken from a Norwegian setting. However, the cost of mm-398 is only available in US $, which makes the converted value, an uncertain rough estimate. A weakness related to the costs is that the cost of stay is only a mean value, and not specific to the patient

group in this study. There are also other potential costs that have not been included in this study, like overhead costs and costs of adverse events. This was done to simplify the model.

6.3 Similar studies

When it comes to mPAC patients who progressed after receiving gemcitabine based treatment there is no standard of care. The trial this study is based on is the only phase III RCT that evaluates a new therapeutic agent in this patient group (Gaddy et al. 2015).

In 2013, A.H. Ko et al published an article based on a multinational phase II study of mm-398 for patients with metastatic pancreatic cancer who had received gemcitabine based first-line treatment. Their results were, a mean overall survival of 5.2 months and a mean progression free survival of 2.4 months. However, there were no comparators in this study, and mm-398 was given as a monotherapy (A.H. Ko et al. 2013).

PharmaEngine conducted a phase II trial where they compared mm-398 monotherapy with Irinotecan monotherapy and Docetaxel monotherapy, as second-line treatment for patients with locally advanced or metastatic gastric cancer. In this study they came to the conclusion that PFS and OS were similar in the three treatment arms (A.C. Roy et al. 2013).

There have been conducted other RCTs of second-line mPAC treatment, but very few included a treatment arm with mm-398. This could be because it is a fairly new drug. The combination of mm-398/5-FU/LV has only been tested in one phase III trial.

6.4 Uncertainty

The parameters used in this study are deterministic values reported without confidence intervals or standard errors. Hence, the standard errors for the costs were based on assumptions. However, the parameter uncertainty was explored through a probabilistic sensitivity analysis and the estimation of the EVPI. The parameters with probably more uncertainty than accounted for are the transition probabilities, as they were derived from survival curves and not individual patient data. Another problem is that there are no other studies of this particular treatment, which makes it difficult to compare the results of this study to others. The results in this study are based on a trial in a controlled environment, with only a couple of hundred patients. However, this was a multinational trial with patients from 14 countries.

6.5 Validation

Face validity was done by checking if the model made sense. The structure of the model was assessed. The model is based on clinical pathways and the decision tree in Figure 8. The decision tree is based on information provided by the Norwegian Directorate of Health and results from clinical trials.

For internal validation, I checked the equations in the model to see if they were consistent. I checked if the transition probabilities added up to 1. In the Markov model, I added a check column, where I added up those alive and those who had died at each cycle. This was done to make sure that there were no mistakes in the equations.

For cross-validation, I could not make any direct comparisons to other studies because to my knowledge, there are no similar studies available at the moment.

For external validity, I compared the fitted Weibull models to the published Kaplan-Meier curves. The movements of the Weibull survival curves were fairly similar to the Kaplan-Meier curves.

7 Conclusion

The results of the economic evaluation indicate that mm-398/5-FU/LV as second-line treatment for mPAC patients is cost-effective at a WTP threshold of NOK 437 247 or higher. The cost per LYG was NOK 37 205 for 5-FU/LV and NOK 124 787 for mm-398/5-FU/LV. The estimated cost per patient is NOK 303 154 in the 5-FU/LV group and NOK 1 301 782 in the mm-398/5-FU/LV group. The estimated LYG is 8.15 with 5-FU/LV and 10.43 with mm-398/5-FU/LV. Hence, mm-398/5-FU/LV generates more LYG and higher costs than 5-FU/LV. The probabilistic sensitivity analysis confirms these results. The EVPI indicates that if the maximum willingness to pay is around NOK 450 000, investments should be made in further research to avoid making a wrong decision. However, this should only be done if the cost of additional evidence is NOK 48 439 or lower.

I believe further research should be made regarding the effects of the treatment on the patient's quality of life. The results of this study should be interpreted with care, due to the fact that it is an explorative study and further research is advised.

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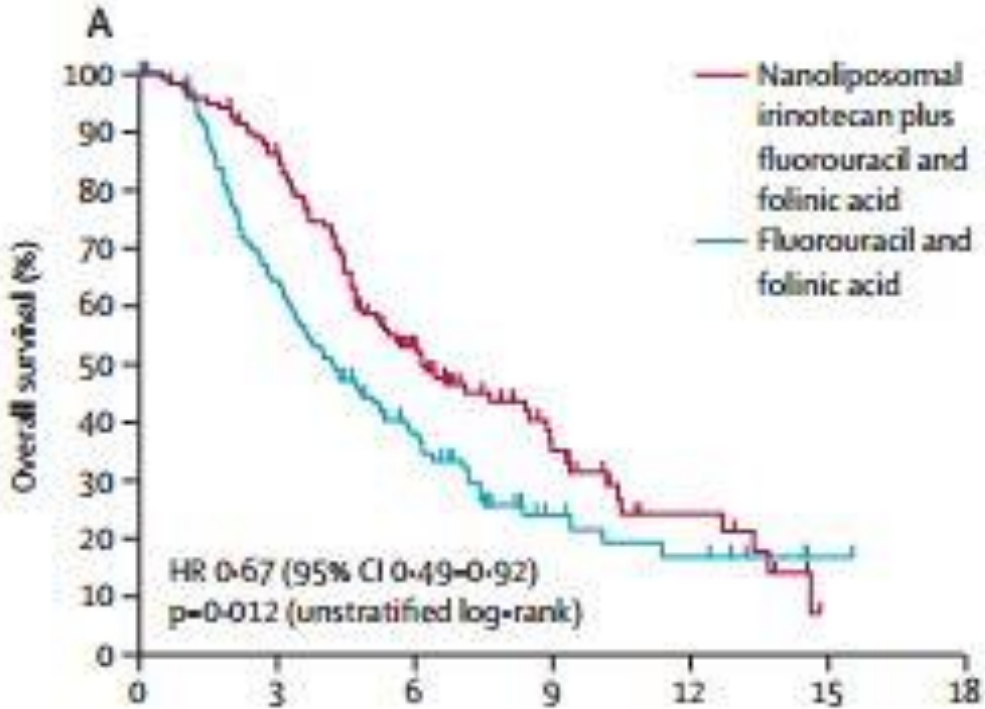
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Appendix I: Kaplan-Meier curves from article

Appendix II: Hoyle and Henley Excel sheet

Start time	Mid time	Mid time	Empirical survival probability S(t)	Weibull est S(t)	Weibull PSA S(t)	Number at risk R(t)	Estimated Number Events D(t,t+1)	D(t,t+1/2), D(t+1/2,t+1)	D(t,t+1/4), D(t+1/4,t+1/2), D(t+1/2,t+3/4), D(t+3/4,t+1)	Estimated Number Censorships C(t,t+1)	C(t,t+1/2), C(t+1/2,t+1)	C(t,t+1/4), C(t+1/4,t+1/2), C(t+1/2,t+3/4), C(t+3/4,t+1)
0.00	0.25		1.0000	1.0000	1.0000	100			5			6
0.50	0.75	0.50	0.9464	0.9671	0.9615	89.0		6	1		12	6
1.00	1.25		0.9354	0.9317	0.9251	82.0			2			6
1.50	1.75	1.50	0.9113	0.8961	0.8902	74.0	10	4	2	24	12	6
2.00	2.25		0.8845	0.8609	0.8568	66			2			5
2.50	2.75	2.50	0.8561	0.8263	0.8248	58.9		9	6		10	5
3.00	3.25		0.7585	0.7927	0.7940	47.7			1			5
3.50	3.75	3.50	0.7396	0.7599	0.7644	41.8	9	1	0	20	10	5
4.00	4.25		0.7396	0.7281	0.7360	37			2			3
4.50	4.75	4.50	0.6961	0.6974	0.7086	32.2		3	1		6	3
5.00	5.25		0.6721	0.6677	0.6823	28.4			3			3
5.50	5.75	5.50	0.5972	0.6390	0.6571	22.8	6	3	0	11	6	3
6.00	6.25		0.5972	0.6113	0.6327	20			2			2
6.50	6.75	6.50	0.5269	0.5847	0.6094	15.9		3	1		4	2
7.00	7.25		0.4918	0.5591	0.5868	13.0			0			2
7.50	7.75	7.50	0.4918	0.5344	0.5652	11.0	4	1	1	8	4	2
8.00	8.25		0.4372	0.5107	0.5443	8			0			2
8.50	8.75	8.50	0.4372	0.4880	0.5243	6.0		0	0		4	2
9.00	9.25		0.4372	0.4662	0.5050	4.0			0			2
9.50	9.75	9.50	0.4372	0.4452	0.4864	2.0	0	0	0	8	4	2
10.00			0.4372	0.4251	0.4685	0						
		0.00										
		0.00										

No Patients at risk at last time point ?
patients risk at last time point
time of censoring of patients at risk at last time point

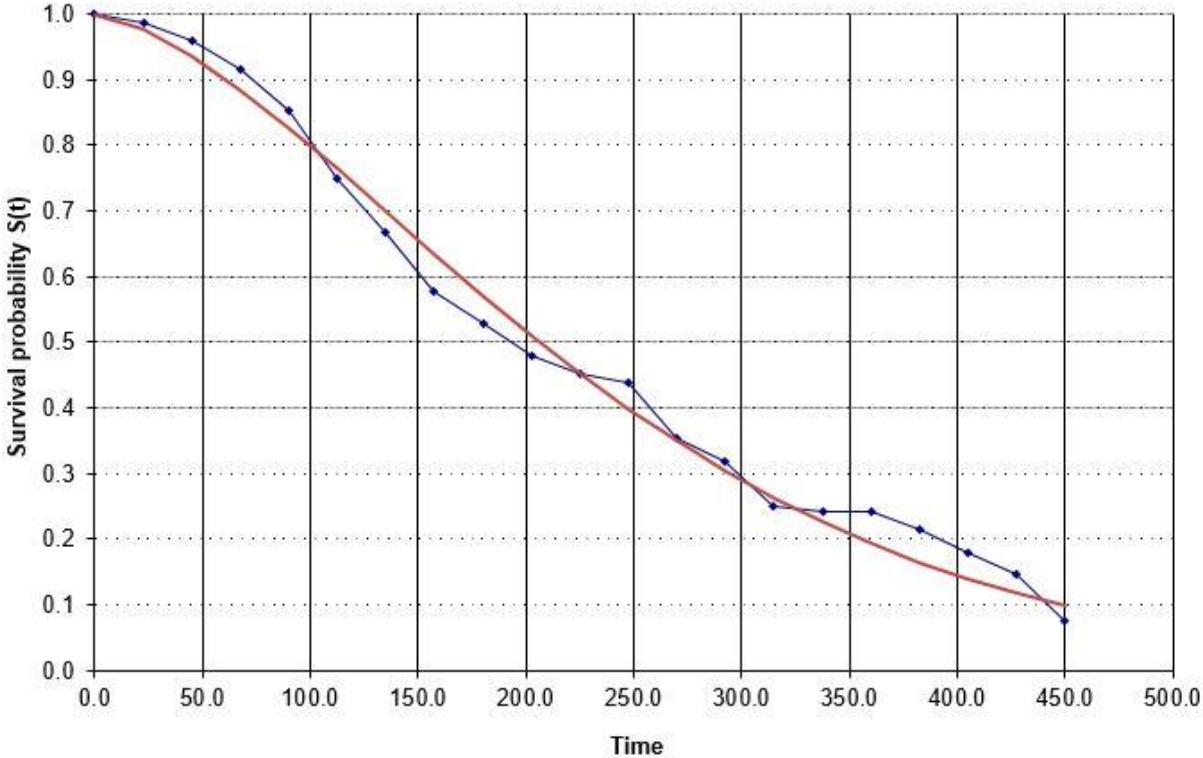| Weibull	Mean	
intercept	2.4468	Pasted from output from "Curve fitting 'R' code"
log(scale)	-0.0793	Pasted from output from "Curve fitting 'R' code"
lambda	0.07074	
gamma	1.08253	

Appendix III: Fitted Weibull curve – Comparator
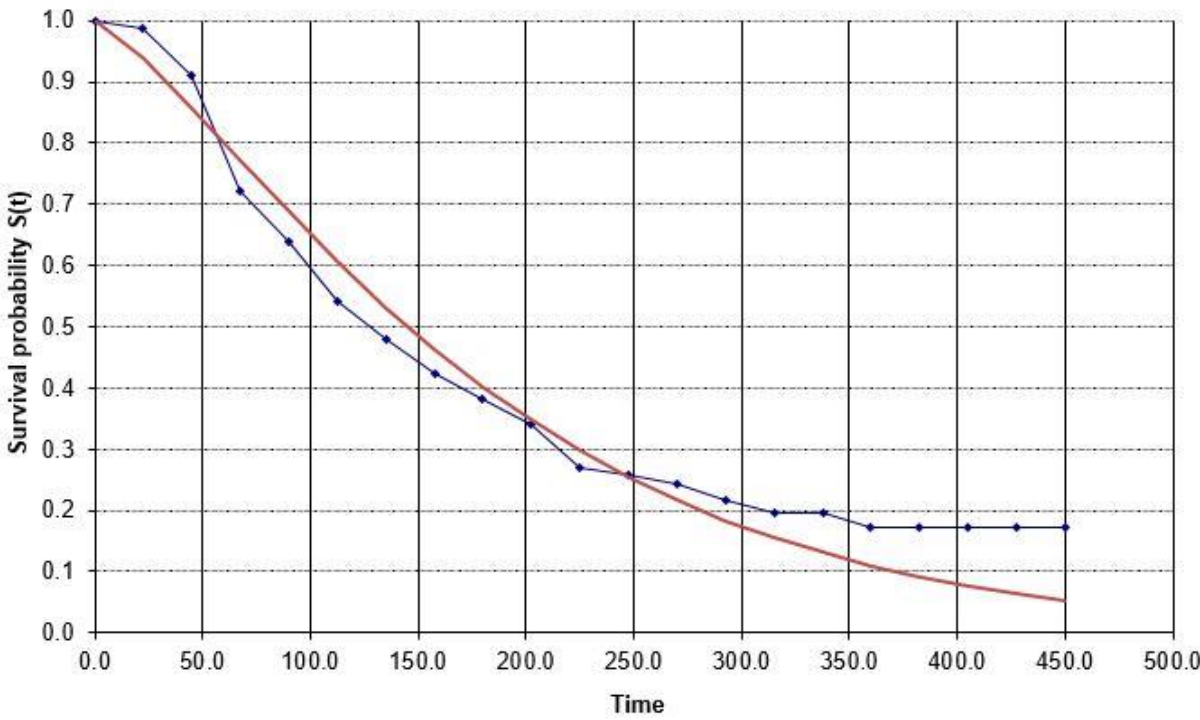
The blue line is the empirical survival probabilities, extracted from the Kaplan-Meier curve from the trial. The red line is the fitted Weibull curve.

Appendix IV: Fitted Weibull curve - intervention

Blue line = Empirical survival probability

Red line = Weibull estimated survival

Appendix V: Parameters-Gemcitabine

Parameter	Value	Confidence interval
Mean OS	6.7	6,0–7,2
Mean PFS	3.7	3,6–4,0
Response	9.40 %	-
Stable	41.50 %	-
Progression	34.50 %	-
Drug cost	NOK 1 600	-

Appendix VI: Formulas used to make the probabilistic model in Excel

Parameter	Probabilistic	Deterministic	Random draw	Alpha	Beta
Cost	gammainv(rand();α;β)	P	x	α	β
tp_S2S	x_1/sum(x_1,x_2)	p1	x_1	r	n-r
tp_S2D	x_2/sum(x_1,x_2)	p2	x_2	r	n-r

- tp_S2S = probability of staying alive

- tp_S2D = probability of dying

- The transition probabilities were calculated for each cycle separately.

- r = event of interest

- n = sample size

- Random draw (tp) = gammainv(rand();α;1)