Atezolizumab as first-line treatment for selected patients with advanced or metastatic urothelial carcinoma

Master Thesis Report

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SUMMARY

Introduction Until recently, there was no acceptable treatment for patients with advanced or metastatic urothelial carcinoma who have relapsed after first-line palliative chemotherapy. Nowadays, anti-PD-1 checkpoint immunotherapy has been introduced as second-line treatment, which have shown promising results of durable benefit over 2 years in the 20% of responding patients. However, response rates to this therapy are low and the treatment is very costly. As, anti-PD-1 checkpoint immunotherapy will likely move towards the first line, it will be ever more vital to identify and solely treat patients who are most likely to respond with immunotherapy, and treat those unlikely to respond with standard chemotherapy. This study aims to decrease both the health burden and the economic burden by preventing overtreatment.

Method A discrete event simulation, representing both the current and alternative treatment pathway, was developed to determine the cost-effectiveness. In the alternative path, a Clinical Decision Algorithm is used to stratify patients between immunotherapy and standard chemotherapy in the first line, based on the biomarkers immunohistochemical expression of PD-L1 in tumor microenvironment, the tumor mutational burden, and RNA expression signatures. The analysis that were performed are a cost effectiveness analysis, where the effectiveness is expressed in quality adjusted life years, and a sensitivity analysis to determine the most influencing parameters.

Results In the alternative pathway, 49% of the patients are stratified for the immunotherapy path in the first line based on their biomarker signature score of response to checkpoint immunotherapy. 14% of the patients will receive immunotherapy because they are chemotherapy ineligible or a biopsy is not possible. The sensitivity of the clinical decision algorithm is 63%, against a specificity of 47%. The average total cost per patient in the current treatment pathway are €92.984, yielding 2.36 Quality Adjusted-Life Years (QALYs). For the alternative path, the average total cost per patient are €75.729, with a QALY result of 2.08. The average cost per QALY are €39.437 for the current pathway and €36.355 for the alternative pathway. The alternative pathway will save on average €17.255 per patient, with a QALY loss of 0.28. For a hypothetical increased response rate to immunotherapy with 20%, the QALY gain is 0.15 and the savings are €8.162 per patient.

Conclusion Targeting immunotherapy as first-line treatment for patients with metastatic or advanced urothelial carcinoma will have a negative effect on the health outcome with a QALY loss of 0.28, but will save €17.255 per patient, which results in a saving of €61.625 per qualy. The incremental savings per QALY are above the willingness to pay line, which indicates a higher cost-effectiveness, however the QALY decrease is high. A higher cost-effectiveness ratio is reached when the response probability for immunotherapy is at least 20% higher in the first line, compared to the response probability in the second line; the QALYs will increase and costs decrease. A higher cost-effectiveness ratio is also reached when the sensitivity and the specificity of the decision model increase, but QALYs are still lower, compared to the current pathway.

PREFACE

In this master thesis report I present my research of selecting patients with advanced or metastatic urothelial carcinoma for immunotherapy in the first-line treatment. This end result of the study Industrial Engineering and Management is also the end of me being a student at the University of Twente. I have always enjoyed my study period, and the new friends that I have met, made it an amazing and unforgettable time.

During my graduation period I had a lot of support and advice, for which I like to show my gratitude. I want to thank my supervisors of the University of Twente Maarten IJzerman and Koen Degeling, for their guidance, feedback, patience and coffee. I also want to thank my external supervisor of the Radboud University Medical Centre dr. Niven Mehra. He has been very helpful to me to understand the difficult matters of metastatic urothelial carcinoma, the current treatment pathway, immunotherapy, checkpoint inhibitors, biomarkers, and so on.

Last but not least I will also thank my family and friends for supporting me during my study and encouragement during my graduation period. Their support helped to keep me motivated and positive during the process.

I am glad and also proud to hereby present my master thesis and I hope you will enjoy reading it!

Stef Wiegink,

June, 2018

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1 INTRODUCTION

1.1 BLADDER CANCER

Bladder cancer (BCa) is the seventh most common cancer in the Netherlands, with approximately 7100 new diagnoses in 2016. It is more common in men than in women (5600 versus 1500 diagnoses in 2016, respectively) (CijfersOsverKanker, 2017). With regard to the type of cell the cancer started in, BCa can be divided into three histological subtypes: urothelial carcinoma (90%), Squamous cell carcinoma (8%) and adenocarcinoma (2%) (Oncoline). This thesis focuses only on urothelial carcinoma (UC), since this is the most common type of bladder cancer, and most evidence is available for UC. Regarding the disease stage, approximately 50% of the new diagnosed cases are non-invasive carcinoma, which means that the carcinoma is still in the transitional epithelium of the bladder (AmericanCancerSociety, 2017a; CijfersOsverKanker, 2017).

Tumours are staged according to the 7th edition of the TNM classification, where T describes the primary tumour, N describes the regional lymph nodes and M describes the distant metastasis (Cancer.net, 2017). The extensive 7th edition of the TNM classification can be found in appendix A.

When the tumour (T) grows into the muscle layer of the bladder wall, the cancer is classified as a muscle invasive carcinoma, in which T2, T3 and T4 stages are distinguished (see Figure 1 for the T stages). In the T2 stage, the cancer has reached the layer of thick muscle, but has not grown through it completely, i.e. the layer of fatty tissue is not reached. In the T3 stage, the fatty tissue is reached. The last and most advanced stage of UC is the T4 stage, in which the cancer has grown completely through all the layers of the bladder. The N describes if, and to how many regional lymph nodes the cancer has spread. When no lymph nodes are reached it will be staged as N0, N1 stands for 1 lymph node infected, and with N2 there are 2 or more lymph nodes infected. When the tumour has metastasis to other parts of the body it is classified as M1, where we distinguish M1a, with metastasis to only non-regional lymph nodes, and M1b, where the cancer has spread to other tissue sites of the body, such as bone or visceral organs. When the tumour is in stage T4, or when the cancer spread to the non-regional lymph nodes or other metastatic sites, we speak of locally advanced or metastatic urothelial carcinoma (mUC) (AmericanCancerSociety, 2017).

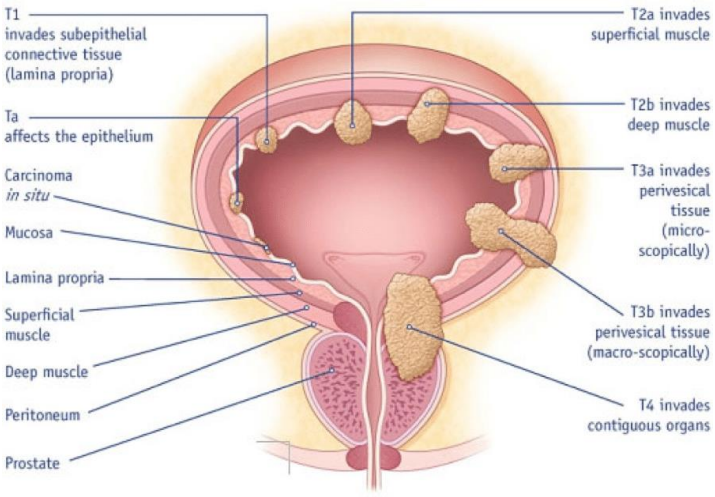

Figure 1: tumour stage (Asurology, 2016)

1.1.1 Treatment and prognosis

The prognosis of UC is strongly correlated with the stage in which the tumour is discovered. The stage is depending of the TNM classification. When the tumour is non-invasive, the applied treatment is transurethral resection (TUR), whereby the tumour will be removed through the urethra. The 5-year survival for patients with non-invasive UC is almost 90% (Anastasiadis & de Reijke, 2012). For patients with T2 or T3 stage tumours (i.e. invasive disease), the most applied treatment is radical cystectomy, whereby the complete bladder will be removed. 5-year survival for patients with T2 or T3 stage tumours is 63% and 46%, respectively (AmericanCancerSociety, 2017b). After a radical cystectomy for mUC, 50% of the patients will develop a metastasis. For these patients, no curative treatment options are available, so anti-cancer treatment is provided to reduce and delay the onset of symptoms (i.e. palliative treatment). If metastases are already present at the time of the diagnosis, radical cystectomy will not be performed and treatment for mUC will be started. Current recommended first-line treatment in the Netherlands for mUC consists of combination chemotherapy of gemcitabine/cisplatin or gemcitabine/carboplatin. Which of both first-line treatment options will be used, depends on the renal function and the performance status of the patient (Bournakis, Dimopoulos, & Bamias, 2011; Oncoline, 2009). Response rates to chemotherapy are high, but duration of response is generally low, with 3-year survival rate is less than 20%. As second-line treatment, after failure of platinum-based chemotherapy, vinflunine has registration in Europe. However, this therapy is associated with high toxicity and, therefore, not widely adopted as standard second-line treatment (McGahan, 2016).

1.1.2 Urothelial carcinoma and Immunotherapy

Recent development in immunotherapy has led to the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approval of the checkpoint inhibitors Pembrolizumab, nivolumab and Atezolizumab as second-line treatment option in mUC, following failure to combination chemotherapy (NationalCancerInstitute, 2017)

Checkpoint inhibitors aim to release the breaks of the immune system by targeting the interaction between the Programmed Cell Death 1(PD-1) and the Programmed Cell Death – Ligand 1 (PD-L1) (AmericanCancerSociety, 2015). The immune system effector cells are mainly cytotoxic T-cells that are trained to distinguish normal cells and foreign cells. These T-lymphocytes are part of a complex immune repertoire of lymphocytes, and play a major role in the fight against cancer. T-cells have several receptors on their surface with different functions. One of these functions is to detect foreign cells by means of assessing the antigens presented on the surface a cell. Those antigens are pieces of degraded protein from within tumour of normal cells. When the code for these proteins, the DNA, has been mutated, aberrant proteins fragments can be presented, that differ between self-antigens. When the immune system recognizes these antigens as “foreign”, the T-cell can be activated and the immune response started. However, T-cells do also have checkpoints that can dampen the immune response, and are important mechanisms to counter auto-immunity. One of these mechanisms is the PD-1-PD-L1 signalling pathway. Immune cells

can have PD-L1 and PD-1 expressions to counteract an inflammatory reaction. PD-L1 also comes to expression on body tissue to protect against autoimmunity. When the PD-1 and PD-L1 proteins interact to each other, the T-cell will be “turned off” and it will not fight the cell.

Some cancer cells also have PD-L1 expression, which prevents the immune system from attacking these cancer cells with PD-L1 expression. Immunotherapy with checkpoint inhibitors aims to obstruct the binding of cancer cells with PD-L1 expression to PD-1 using monoclonal antibodies. Some examples of checkpoint inhibitor agents are: nivolumab (PD-1 inhibitor), Atezolizumab (PD-L1 inhibitor), and Pembrolizumab (PD-1 inhibitor) (DUOS, 2016). Recent phase II and phase III studies with randomized controlled trials (Imvigor210 and IMvigor211) have shown promising results in unselected patients, illustrating response rates of 20% to 30% with durable response of over two years (Balar et al., 2017; Powles et al., 2017; Rosenberg et al., 2016). Although introduction of these agents is an important asset to the therapeutic armamentarium of metastatic or unresectable urothelial carcinoma patients, treating unselected patients will have a major impact on health-care burden, in terms of health outcomes and economic outcomes due to overtreatment and high cost of the treatment (Heijden van der, 2016). Since Roche-Genentech have invested heavily in biomarker development for atezolizumab, this thesis has focused on atezolizumab as agent for atezolizumab the second-line treatment for mUC, as most translational evidence is available for this checkpoint inhibitor.

1.1.3 The use of biomarkers to predict response

Literature shows that several factors affect the response to atezolizumab, of which PD-L1 score, mutational load and The Cancer Genome Atlas (TCGA) signature are the most distinctive (Rosenberg et al., 2016). What these biomarkers are and how they affect the response to atezolizumab will be explained in chapter 2.3. As said before, it is important to avoid overtreatment with atezolizumab by targeting treatment to patients who are most likely to benefit using these biomarkers. However, although data on response rates according to each of these biomarker separately is available, response rates for combinations of these biomarkers are not. Consequently, it is not yet possible to target atezolizumab in an optimal way.

1.1.4 Atezolizumab as first-line treatment

Until recently, no suitable treatments were available for metastatic or advanced urothelial carcinoma after chemotherapy, but developments in the field of immunotherapy have changed this stalemate. Immunotherapy becomes more and more important in the treatment of several types of cancer, including mUC, as the clinical outcomes are dramatically improved compared with the conventional chemotherapy. Currently atezolizumab is used as second-line treatment for patients who have progressed following treatment with chemotherapy, with promising and durable results (Rosenberg et al.,

2016). Patients with partial and complete responses have durable responses that last significantly longer in comparison to chemotherapy.

If it would be possible to select for responsive patients for atezolizumab, it would be most beneficial when atezolizumab could be given as first-line treatment, as, their conditions of non-effective chemotherapy could be withheld in those patients. As response rates are low, it may prove vital to predict the response probability for each patient in real-time, to shift atezolizumab from the second-line treatment to the first-line treatment., Only patients who are most likely to respond to Atezolizumab, or patients who are unfit for chemotherapy, will be eligible for treatment with atezolizumab. The decrease of overtreatment will also result in a decrease of unnecessary health and economic burden. Patients who do not respond to first-line treatment with immunotherapy, will receive second-line treatment with chemotherapy.

1.2 RESEARCH

1.2.1 Problem statement

Current clinical pathways of treatment of advanced or metastatic urothelial carcinoma at present mandates first line doublet chemotherapy followed by second-line immunotherapy, in those with adequate organ function and/or performance status.

Management of the current clinical pathway results in a substantial amount of overtreatment (Larkin et al., 2015). All-comers receive second-line immunotherapy, while only a minority will respond (Rosenberg et al., 2016). Approximately 20% of patients treated with checkpoint immunotherapy have long-term responses.

Treatment with checkpoint inhibitors, will commonly cause side effects like severe headaches, diarrhoea, and less commonly serious immune-related side effects (such as pneumonitis and colitis), which leads to a decrease in quality of life (M. A. Postow et al., 2015). Another challenge for atezolizumab is that the treatment is very costly, and can cost up to €6.000,= per patient per month (Andrews, 2015). Summarized, the overtreatment of mUC patients with atezolizumab leads to both economic and health burdens (Larkin et al., 2015; Weber, Hodi, Wolchok, & Topalian, 2016).

A clinical decision algorithm is necessary to target the patients who are most likely to respond to atezolizumab. If these patients could be selected for treatment in the first-line, a more sustainable and cost-effective treatment pathway would be established (Blank, Haanen, Ribas, & Schumacher, 2016). Although a single predictive biomarker for treatment allocation is not yet available, multiple sub-optimal biomarkers with predictive characteristics are, though these have not (all) been tested prospectively.

1.2.2 Objective

This thesis aims to assess whether a treatment targeting strategy of responsive patients with metastatic or advanced urothelial carcinoma for immunotherapy in the first line can reduce the health economic burden. The health economic burden in the first line is caused by the high amount of overtreatment, which results in reduction of quality of life and increase in costs. In order to reach the objective, a cost-effectiveness model will be developed in which we compare the current standard of treating all comers with chemotherapy in the first line followed by immunotherapy in the second-line treatment, to the alternative path in which we target immunotherapy in the first line based on (putative) predictive biomarker values.

Our model is based on available published and unpublished data; when no data was available best possible assumptions were made. Therefore the health-economic model presented in this thesis should be seen as hypothetical model based on current data obtained in the time-frame writing this thesis.

1.2.3 Research question and sub questions

The research question for this master thesis is defined as follows:

"What is the expected health economic impact of selecting for responsive patients for immunotherapy in the first line setting in patients with metastatic urothelial carcinoma using a combination of biomarkers, in comparison to standard therapy that consists of treatment of all comers with chemotherapy in the first-line treatment followed by immunotherapy in the second line?"

In order to answer the research question and achieve the objective, several sub questions are defined:

1. What is immunotherapy and can it improve the life expectancy off patients with advanced or metastatic urothelial carcinoma?
2. What does the current clinical treatment pathway of metastatic urothelial carcinoma look like, and where does immunotherapy fit in?
3. Which biomarkers are available to predict response for atezolizumab in patients with advanced or metastatic urothelial carcinoma, and how do they affect response?
4. How can these biomarkers be combined to predict the response to Immunotherapy?
5. How can we model de process of targeting patients with mUC for immunotherapy in the first-line treatment?

1.2.4 Research plan

Sub-research question 1 is answered by a combination of expert opinions and literature research. Expert opinions are necessary because a variety of treatment guidelines are available in literature. Sub-research question 2 and 3 are answered by literature research. Sub-research question 4 is answered by knowledge from previous sub-questions and expert opinions. To answer sub-research 5, a model is needed to estimate the health economic impact of targeting patients with mUC for atezolizumab in the first-line treatment.

2 LITERATURE STUDY

In this section, answers will be given to the first sub questions of the research. At first the matter of immunotherapy is discussed, where after the current treatment process of mUC is discussed and at the end the predictive biomarkers for immunotherapy in patients with mUC are explained.

2.1 WHAT IS IMMUNOTHERAPY

What is immunotherapy and can it improve the life expectancy off patients with advanced or metastatic urothelial carcinoma?

Cancer immunotherapy is a treatment for cancer that focuses on different parts of the patient's own immune system to support its fight against cancer. Immunotherapy can focus on stimulating the immune system to operate harder or in a more efficient way to fight the cancer cells, or it can give the immune system additional components to support and strengthen the immune system. In the past 20 years, different forms of immunotherapy became an important treatment in the fight against cancer (AmericanCancerSociety, 2016).

2.1.1 The immune system

The immune system consists of a complicated network of organs, cells and substances to help the body from being infected by viruses, bacteria, fungi or parasites, and is therefore one of the most complex systems of the human body (M. Postow, Wolchok, Atkins, & Ross, 2016). The immune system controls each cell of the body and raises an alarm if substances or cells are not recognized. If cells are seen as foreign, they will be attacked and destroyed by the immune system. Cancer cells can be destroyed as well, provided that they are recognized by the immune system, since cancer cells have the ability to "hide" from the immune system so the cells can divide uncontrollably. It is also possible that the immune system recognizes the cancer cells, but it is not strong enough to fight it, because of the advanced status of the cancer (IQWiG, 2016). To help the immune system to recognize or fight cancer, researchers came up with different methods to support the immune system: immunotherapy.

2.1.2 Immunotherapy types

The immune system can be supported in different ways. The most important types of immunotherapy that are used nowadays are stated the following section. The types of immunotherapy that are not taken into account are: Cytokines, vaccines to treat cancer and adoptive cell transfer.

2.1.2.1 Monoclonal antibodies:

The immune system fights foreign cells in multiple ways, one of which is by attaching antibodies to the antigens of the foreign cell. Each sort of cell presents specific antigens on their cell membrane. The antibody searches for an antigen to attach with. Once the antibody is attached to the antigen, it collects other cells of the immune system to attack

the foreign cell. Antibodies can be designed to attach to a specific antigen, for example the once that are found on cancer cells. When the right antibodies are released in the body, they will attach to the cancer cell, so other parts of the immune system are recruited to destroy the cell (Weiner, Dhodapkar, & Ferrone, 2009).

2.1.2.2 Immune checkpoint inhibitors

As said before, the immune system is able to tell the difference between cells that are normal and cells that are foreign. In the process of detecting foreign cells, the immune system uses receptors on their surface. There are many different receptors on the membrane of normal cells, cancer cells and immune cells. With these receptors the immune cells "communicate" with other cells. Stimulatory receptors on the T-cells trigger the T-cell to attack the other cell when activated. Other negative receptors, or checkpoints, will signal the T-cell to stop the attack. One of the checkpoints that acts as an off-switch is the protein called PD-1, which can bind to the ligand PD-L1 that is found on normal cells and some cancer cells. When cancer cells have lots of PD-L1 ligands on their membrane, it can inhibit an effective anti-cancer reaction from the immune system. Monoclonal antibodies can be used to attach to either PD-1 or PD-L1, so the interaction between PD-1 and PD-L1 cannot take place. In Figure 2, the normal situation is shown in the left picture, in the right picture you can see that the interaction between PD1 and PD-L1 is blocked by the Anti PD-L1 and anti PD-1 antibodies. When this interaction cannot take place, the cancer cell is not able to "tell" the T-cell to stop the attack (Doemling, Konstantinidou, Zarganes-Tzitzikas, Magiera, & Holak, 2017) .

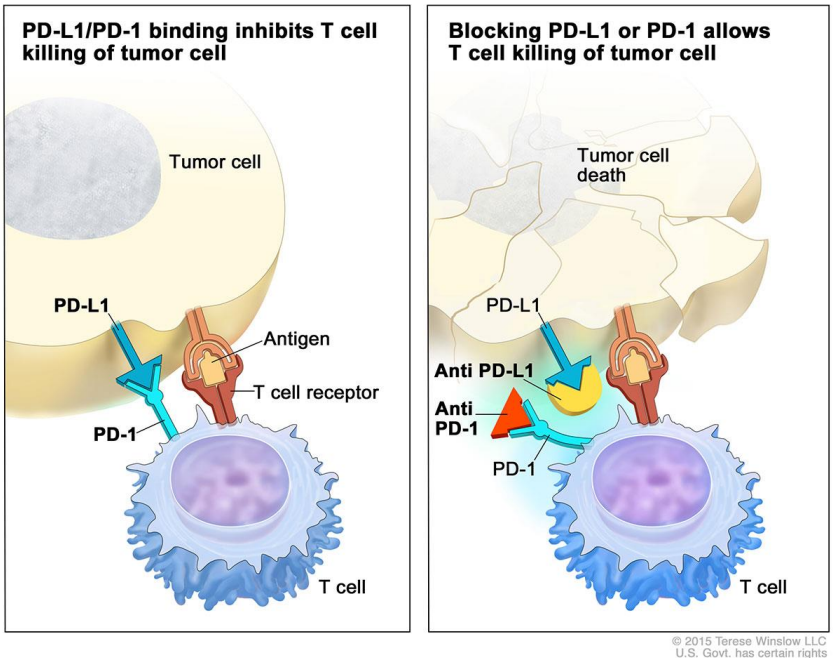

Figure 2: the PD-1 - PD-L1 interaction (NIH, 2016)

2.1.3 Atezolizumab

This thesis focuses on the treatment of mUC with atezolizumab, which is a monoclonal antibody and falls in the category of checkpoint inhibitors. Atezolizumab binds specific to the Programmed Death-Ligand 1 (PD-L1) that is located on the membrane of the tumour cell. Atezolizumab was first tested in clinical trials in 2015, for several solid tumour types. In 2016 it gained approval by the FDA for non-small cellular lung cancer and urothelial cancer. In addition to the benefit of the durable response, there are also disadvantages to

treatment with atezolizumab, such as adverse events. Some of these adverse events are severe, including: pneumonitis, hepatitis, colitis, nervous system problems, inflammation of the eyes, severe infections, and severe infusion reactions. The most common side effects of atezolizumab, however, are less severe: feeling tired, decreased appetite, nausea, constipation, diarrhoea, and fever (GenentechUSA, 2018).

2.2 THE CURRENT PATHWAY

What does the current clinical treatment pathway of metastatic urothelial carcinoma look like and where does immunotherapy fit in?

In this section we discuss the current treatment step by step. At first we discuss the first-line treatment, which consists of different forms of chemotherapy, depending on the patient's condition. Thereafter we discuss the second-line treatment which is immunotherapy. At the end we will discuss the assessment of the tumour growth, which is important to decide whether the treatment continues or stops.

2.2.1 First-line treatment

In the current situation, the first-line treatment of locally advanced or metastatic urothelial carcinoma (mUC) depends on the condition of the patient(de Vos & de Wit, 2010). There are two important factors that determine the patient's condition: 1) the renal function and 2) the performance status. The renal function is defined in terms of creatinine clearance in millilitres per minute, whereby a higher creatinine clearance means a better renal function (de Vos & de Wit, 2010). According to the creatinine clearance, patients are divided into three groups:

1. Creatinine clearance below 30 ml/min (severe renal impairment)
2. Creatinine clearance between 30ml/min and 60ml/min (mild renal impairment)
3. Creatinine clearance above 60ml/min (normal renal function)

The performance status (PS) is defined by the European Cooperative Oncology Group (ECOG) and is scaled from 0 (i.e. fully active patient) to 4 (i.e. completely disabled patient) (Galsky et al., 2011). By combining the renal function and the PS, patients are divided into three treatment groups that are used to select different regimens of chemotherapy or immunotherapy for first-line treatment. Those who receive first-line treatment with immunotherapy are considered unfit to receive chemotherapy. Below in Figure 2 a schematic representation of the current treatment process is shown, thereafter the treatment per patient group will be explained.

2.2.1.1 Cisplatin eligible group

The total population includes 50% cisplatin eligible patients. The cisplatin eligible patient group contains the patients with the best condition, i.e. a PS of 0 or 1 and a creatinine clearance of 60 ml/min or higher. In this group the most effective combination chemotherapy contains cisplatin. Formerly the standard cisplatin based chemotherapy

was a combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), but currently the combination of gemcitabine and cisplatin (Gem/Cis) is preferred since it has similar effectivity with less toxicity (Kaimakliotis et al., 2016). Patients will be treated with (a maximum of) 6 treatment cycles of 3 weeks where each treatment cycle consists of gemcitabine 1,000mg/m² on days 1 and 8, and 70mg/m2 cisplatin on day 1. For treatment with cisplatin, a hospital admission is necessary, gemcitabine treatment is possible in a polyclinic treatment. Costs for each cycle are approximately €3000,=, including medicine and treatment (Mehra, 2018). Every three months the treatment will be evaluated. Without progression, the patient stays in follow up. When progression occurs after 12 months, the patient will be re-challenged with the same chemotherapy regimen. If progression occurs within 12 months, the patient will receive second line therapy. How progression is defined will be described later on in this chapter. The response for this chemotherapy is up to 70%, however, the duration of response is only short-lived with a median progression-free survival of only 7 to 8 months (Maase et al., 2000; Oncoline, 2009).

2.2.1.2 Cisplatin ineligible group

Not all patients can receive cisplatin, due to the toxicity of the treatment. If the renal function and PS are not good enough, cisplatin will probably do more harm than good (Maase et al., 2000). Approximately 45 % of the total population is cisplatin ineligible which means they have a PS of 2 or higher and/or a creatinine clearance between 30ml/min and 60ml/min (Bournakis et al., 2011). An alternative for Gem/Cis is a combination of gemcitabine and carboplatin (Gem/Carbo) which has a more tolerable toxicity profile, but with inferior treatment outcome compared to Gem/Cis. Patients will be treated with 6 treatment cycles of 3 weeks, where each treatment cycle consists of Gemcitabine 1000 mg/m² and carboplatin AUC- 4.5 on day 1. The costs of a gem/carbo cycle are approximately €1000. Treatment evaluation will be similar to the evaluation for treatment with Gem/Cis (see Table 1).The response rate for chemotherapy with Gem/Carbo is 36% with a median progression free survival of 5,8 months (De Santis et al., 2012; Park et al., 2013; Sella & Kovel, 2012).

2.2.1.3 Chemotherapy ineligible

In approximately 5% of the patients with metastatic urothelial carcinoma, the patient is ineligible for any platinum-containing chemotherapy regimen due to either a renal function less than 30ml/min, with high likelihood of sever toxicity and kidney failure due to chemotherapy. For those patients the treatment with immunotherapy is nowadays a good alternative (see second line treatment) (Bournakis et al., 2011).

2.2.2 Second line treatment

Formerly, patients who relapsed after chemotherapy, had no good treatment option left. Vinflunine has registration as second line treatment, but due to high toxicity it is rarely used. Nowadays checkpoint inhibitors, such as atezolizumab are used as second line treatment for patients who relapsed after chemotherapy (McGahan, 2016).

Patients will receive a fixed dose of 1200mg atezolizumab intravenous over 1 hour every 21 days. Every three months, tumour assessment will be performed. If there is no progression, the immunotherapy will continue. If progression is observed the immunotherapy will be aborted and the patient will go into the best path of care, because no other treatment options are left. Treatment with atezolizumab is a hugely expensive treatment with monthly costs of approximately €6000, according to dr. Niven Mehra of the Radboud Universitair Medisch Centrum.

2.2.3 Best Path of Care

When no other treatment options are left, the patient is palliative, and will receive the Best Path Of Care (BPOC).

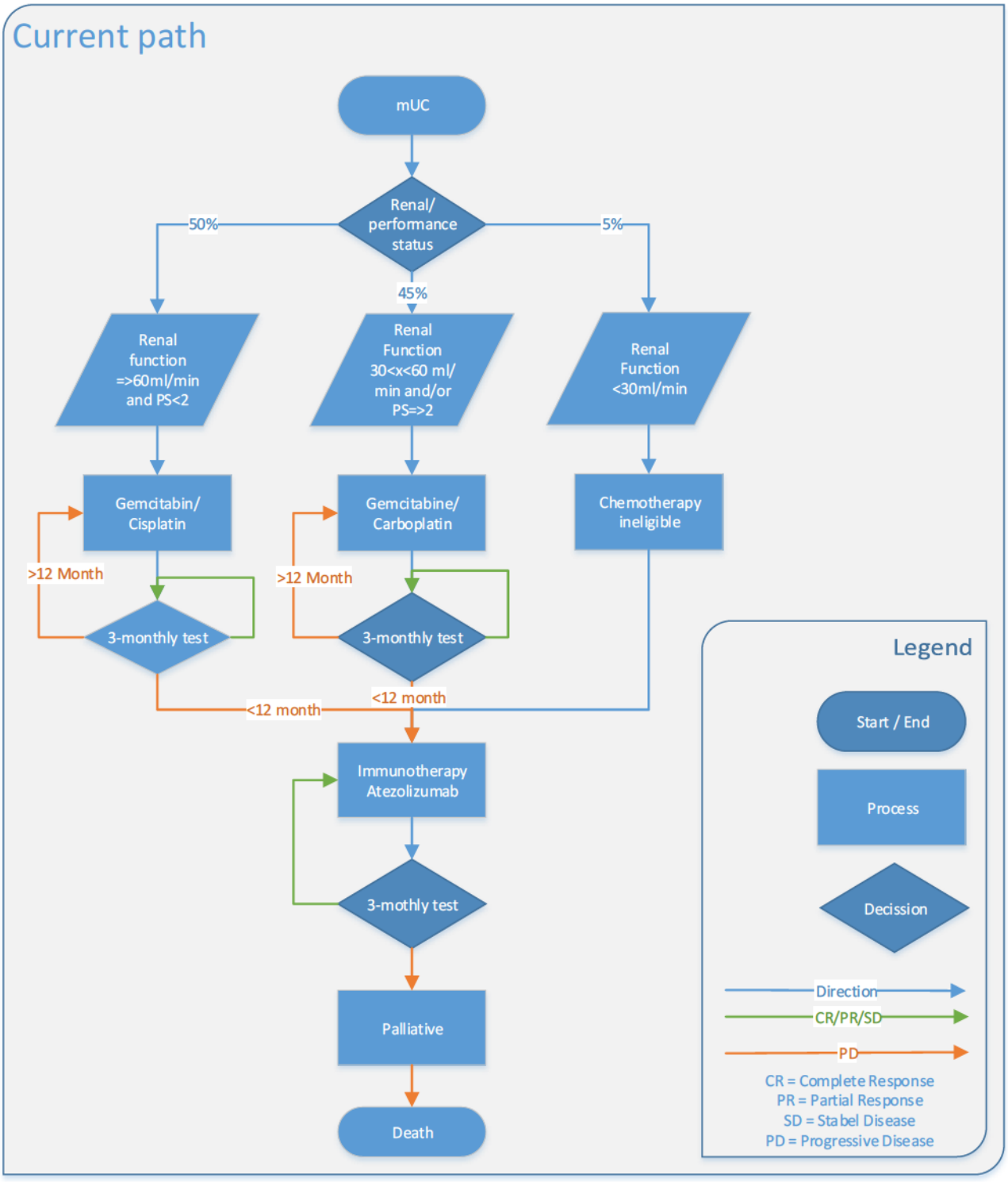

Figure 3: current Treatment pathway

2.2.4 Tumour Assessment

Tumours will be assessed according to the response evaluation criteria in solid tumours 1.1 (RECIST 1.1) criteria. The RECIST criteria help to objectively assess the response to a therapy, by a predefined set of rules. In short, the healthcare professional selects to a maximum of 5 best measurable lesions, with a maximum of two per organ system. For all metastatic lesions except for nodal metastases the longest diagonal of the lesion is measured; for nodal metastases the shortest perpendicular axis is measured. The measured lesions are defined as target lesions, and the sum of those pre-defined target lesions are always defined in all following tumour assessments. To assess the tumour response, the sum of target lesions will be compared to baseline, and the percentage changes and its subsequent response is defined in the table (Eisenhauer et al., 2009).

Tumour assessment	Change in tumour size
Progressive disease (PD)	>20%
Stable Disease (SD)	<20% to <-30%
Partial Response (PR)	<-30%
Complete Response (CR)	-100%

Table 1: Tumour assessment wit RECIST 1.1

2.3 BIOMARKERS TO PREDICT RESPONSE FOR ATEZOLIZUMAB

Which biomarkers are available to predict response for atezolizumab in patients with advanced or metastatic urothelial carcinoma, and how do they affect response?

Clinical trials showed that the response to atezolizumab is influenced by several factors. The most studied biomarkers to date from literature are the PD-L1 expression in the tumor, mutational load, and The Cancer Genome Atlas (TCGA) RNA signature (Blank et al., 2016). These three biomarkers can be tested by running lab tests on a biopsy of the tumor. However, in 10% of the patients in is not possible to take a biopsy of the tumor, and therefore, the biomarker values cannot be determined. When a biopsy is possible, patients will be assigned, based on their biomarker values, to either the immunotherapy arm (alternative pathway), or the chemotherapy arm (current pathway). In the next section those biomarkers will be described. For the extensive data according to the biomarkers PD-L1, ML and TCGA signatures, see chapter 4.1 Inputs, and Appendix B.

2.3.1 Pd-l1 Expression

When PD-L1 on the tumour cell binds to PD-1 on the T-cell, the T-cell will not engage to attack the cancer cell. Atezolizumab focusses on disturbing the interaction between the binding of PD-L1 to PD-1, by binding to PD-L1. The PD-L1 expression is expressed in the percentage of PD-L1 positive immune cells and is divided into 3 groups:

IC0: PD-L1 expression smaller than 1%

IC1: PD-L1 expression between 1% and 5%

IC2/3: PD-L1 expression above 5%

The higher the percentage of PD-L1 expression, the higher the response probability to atezolizumab. The IC score is assessed by a test which costs €300. In the table below, response rates are shown from the Rosenberg et al. (2016) paper.

	Patients, n	Objective response rate, n (% [95% CI])	Complete response	Partial response	Stable disease	Progressive disease
RECIST version 1.1 criteria by independent review						
IC2/3	100	26 (26% [18–36])	11 (11%)	15 (15%)	16 (16%)	44 (44%)
IC1/2/3	207	37 (18% [13–24])	13 (6%)	24 (12%)	34 (16%)	107 (52%)
All patients	310	45 (15% [11–19])	15 (5%)	30 (10%)	59 (19%)	159 (51%)
IC1*	107	11 (10% [5–18])	2 (2%)	9 (8%)	18 (17%)	63 (59%)
IC0*	103	8 (8% [3–15])	2 (2%)	6 (6%)	25 (24%)	52 (50%)

Table 2: IC score and response (Rosenberg et al., 2016)

2.3.1.1 Mutational Load

The mutational load is the number of mutations in a tumour cell per megabase of coding DNA (L. B. Alexandrov et al., 2013). Patients with a higher mutational load are more likely to respond than patients with a low mutational load. This is because the chance that the immune system may recognize a tumour cell as foreign, by aberrant neo-antigen expression on its surface, is higher in patients with more mutations in the protein code. Therefore the tumour cell is better recognizable for the immune system as the mutational burden increases. mUC has the fourth highest mutational load of all cancer types. Only melanoma, lung squamous cell carcinoma and lung adenocarcinoma have a higher average mutational load (L. Alexandrov et al., 2013). In the picture on the right, the relation between mutational load and response is shown. The mutational load is assessed by a test which costs €2,500.

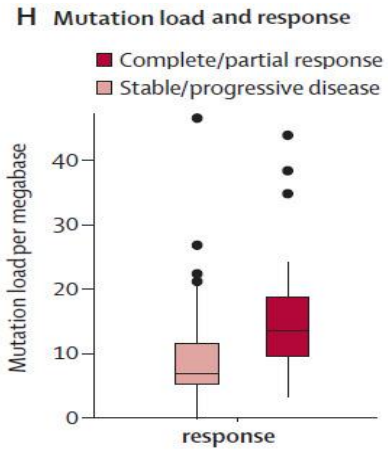

Figure 4: MUTATIONAL LOAD AND RESPONSE (ROSENBERG ET AL., 2016)

2.3.1.2 TCGA signature

The third and last biomarker that is taken into account in this thesis is the TCGA RNA signature. The seminal paper by the TCGA group, assessed the transcriptome of patients with mUC, and was able to divide patients on tissue of origin, with either more luminal (outside of the bladder wall) or basal signatures (inside of the bladder wall) (Choi et al., 2014) . The TCGA signatures are divided into 4 subgroups, subgroup 1 and 2 are the luminal TCGA signatures and subgroup 3 and 4 are the basal subgroups. Both cohorts in the imvigor210 study showed a significant higher response in TCGA group 2 compared with the other subgroups (Aggen & Drake, 2017; Rosenberg et al., 2016). The TCGA signature is assessed by a test that costs €300.

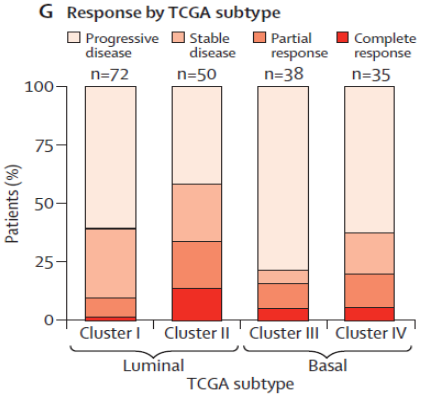

Figure 5: TCGA and RESPONSE (ROSENBERG ET AL., 2016)

3 METHOD

In the first part of this section, it will be explained how the biomarkers can be combined to target patients for immunotherapy, or chemotherapy. In the second part, we will explain how the current and alternative pathway for patients with mUC are modelled.

3.1 HOW CAN THE BIOMARKERS BE COMBINED?

As said in the previous section, a clinical decision algorithm is necessary to decide whether the patients should receive immunotherapy or chemotherapy in the first-line treatment. Ideally this is a response prediction model, but because there is no publically available patient level data, this paper uses a clinical decision algorithm.

3.1.1 The clinical decision algorithm

In Figure 6 this clinical decision algorithm is shown schematically. The patients who are chemotherapy ineligible will be directed to the immunotherapy arm immediately, because there are no other treatment options available. Patients in whom a biopsy is not possible, will be directed to the immunotherapy as well, because a biopsy is necessary to determine the biomarker values and it is unethical to not provide immunotherapy for these patients.

The decision algorithm is based on the biomarkers PD-L1 expression, Mutational load, and TCGA signatures. The values of those three biomarkers can be obtained by running lab tests on a fresh biopsy of the cancer. In Table 3, the estimated costs for the lab tests, given by dr. Niven Mehra, are listed.

Test	*Costs*
Biopsy	€600
PD-L1	€300
Mutational Load	€2500
TCGA signature	€300

Table 3: costs for biomarker assessment (Dr. Niven Mehra)

In the scheme below Figure 6: Clinical decision algorithmFigure 6 a stepwise model, based on the biomarkers, is given to select patients for immunotherapy or chemotherapy in the first line.

The first biomarker to be considered is the PD-L1 expression, which is divided into the groups IC0, IC1 and IC2/3. The IC2/3 group will receive immunotherapy without running other tests, because the IC2/3 group gives the highest response rates for the most important biomarker. When a patients IC-score is 0 or 1, additional biomarker tests need to be performed.

The second biomarker to be considered is the mutational load. A cut-off point of 10 mutations per megabase is chosen, because this is the value of the lower quartile for the non-responders. This value is chosen so 75% of the non-responders will not be selected, while approximately 60% of the responders will. When a lower value is chosen for the

mutational load, the amount of non-responders that will be selected for immunotherapy will increase, and so will the costs.

The last biomarker in the clinical decision algorithm is the TCGA signature. Only patients with a TCGA signature subtype 2 will be selected for immunotherapy. Patients with subtype 2 are most likely to respond, with a rate of patient benefit of around 60% (response rate up to 35 % and a stable patient percentage of 25%). In patients with subtypes 1, 3, and 4, response rates are significantly lower (10, 16, and 20 % respectively (Rosenberg, 2016)), and, therefore, they will not be selected for immunotherapy.

The IC1 group will receive immunotherapy as well, given a mutational load of 10 mutations per megabase or more or TCGA subtype 2, where the mutational load is tested first.

For the patients in the IC0 group, immunotherapy is given only if the mutational load is higher than 10 mutations per megabase, and the TCGA subtype is 2.

There are 6 subgroups of patients who receive atezolizumab, these subgroups, including their characteristics, are listed in Table 4.

Group	PD-L1 expression	Mutational Load	TCGA subtype
1	IC23	Non relevant	Non relevant
2	IC1	>11	Non relevant
3	IC1	<11	Subtype 2
4	IC0	>11	Subtype 2
5	Chemotherapy ineligible		
6	Biopsy not possible		

Table 4: patient groups for atezolizumab arm

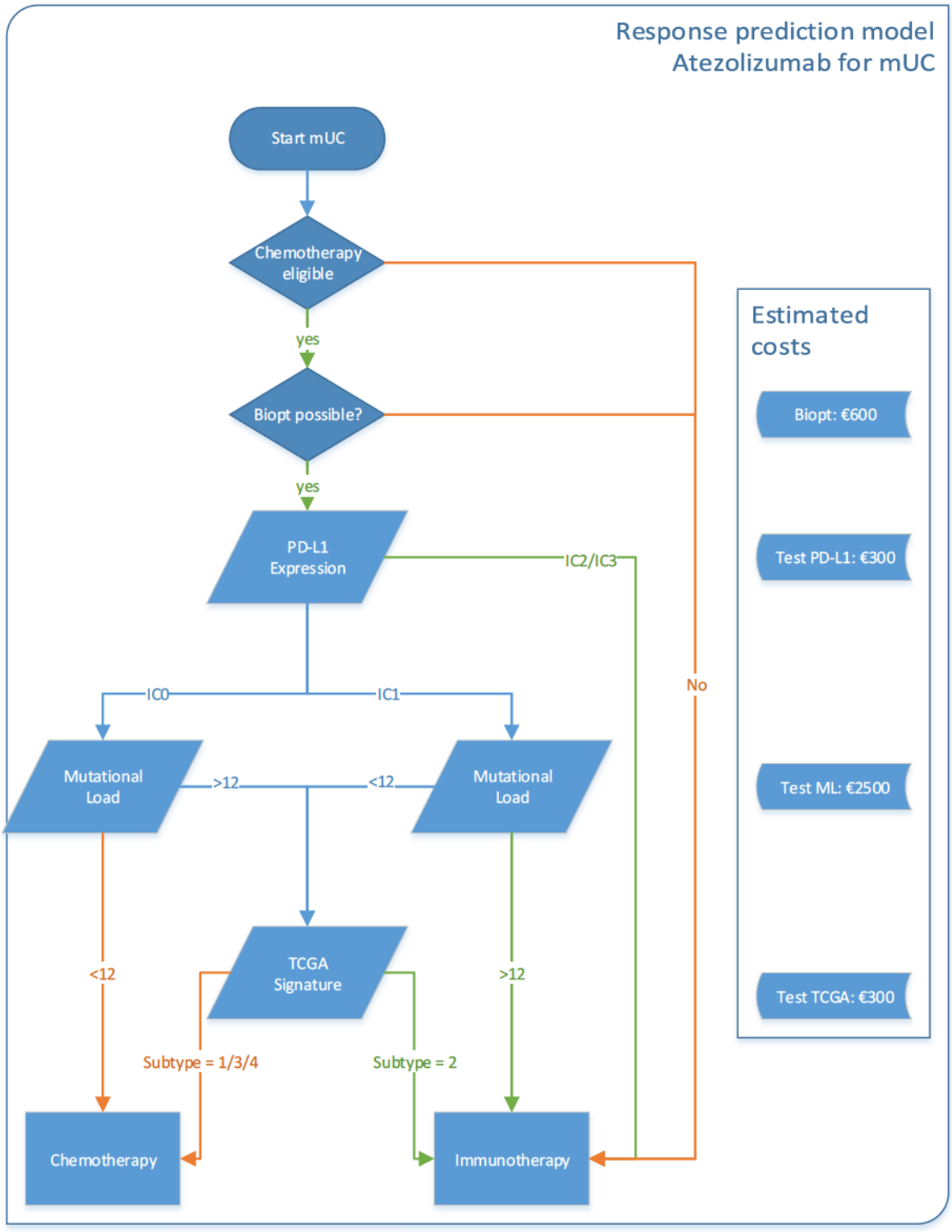

Figure 6: Clinical decision algorithm

3.2 THE ALTERNATIVE PATHWAY

What does the pathway look like for targeting patients with mUC for immunotherapy in the first-line treatment?

The objective is to model the treatment process of targeting atezolizumab in the first-line for patients with metastatic urothelial carcinoma. This alternative path is developed in cooperation with dr. Mehra.

A clinical decision algorithm as seen in the previous chapter, is used to decide whether a patient receives immunotherapy or chemotherapy in the first line. The treatment steps for the alternative path in terms of Gem/Cis, Gem/Carbo and immunotherapy are the same as in the current path, except for the sequence in which they appear. In the figure on the next page, a simplified scheme is shown for the alternative path. In our model, patients who are ineligible for immunotherapy in the first line, are also ineligible for immunotherapy in the second line, since we consider the probability of response for those patients too low. For the patients who do not respond, or relapse after response to immunotherapy, chemotherapy is initiated. By means of this model, the patients who will most likely not respond to atezolizumab, will be filtered out to save costs and prevent unnecessary toxicity.

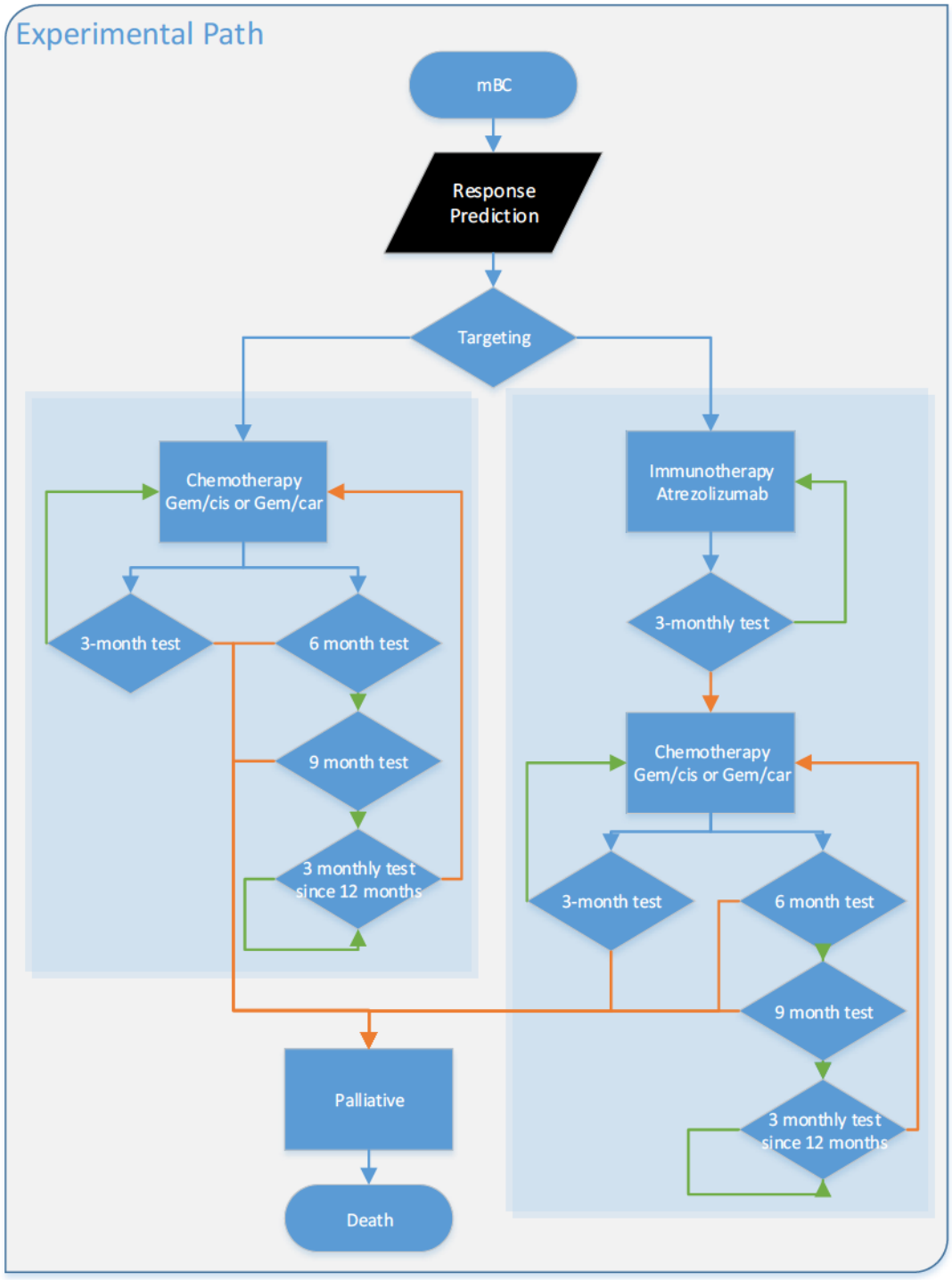

Figure 7: Current Path

In this scheme the patients for the different sorts of chemotherapy combinations are merged, to keep the pathway clear. Obvious, the condition of the patient in terms of renal function and performance status decide which chemotherapy is suitable for the patient.

4 THE MODEL

How can we model de process of targeting patients with mUC for immunotherapy in the first-line treatment?

In this chapter we will discuss how the model was created to estimate the cost-effectiveness of targeting atezolizumab in the first-line treatment for patients with mUC, compare to current treatment. In the first section of this chapter, the input and output measures of the model will be discussed, where after the discrete event simulation model will be explained.

4.1 INPUT

In this section all the input parameters are discussed and how they were obtained. The characteristics provided to the hypothetical patients are based on probabilities from literature and expert opinions. For the model the following inputs are used:

Study population.

The study population that is used in this paper are patients who are newly diagnosed, aged 18 years or older, with metastatic or advanced urothelial carcinoma. For this paper we do not look to previous treatments as transurethral resection or radical cystectomy, because of the lack of patient-level data.

Chemotherapy ineligible / Cisplatin ineligible

Whether a patient is eligible for a chemotherapy treatment depends on the renal function and the performance status of the patient. As said in the literature study we can divide the patients into 3 groups: the Cisplatin eligible group, the Cisplatin ineligible group and the chemotherapy ineligible group. Table 5: Chemotherapy group(Maase et al., 2000) gives the corresponding percentages for the population.

Chemotherapy group	*% of study population*
Cisplatin eligible	55%
Cisplatin Ineligible	40%
Chemotherapy ineligible	5%

Table 5: Chemotherapy group(Maase et al., 2000)

Biopsy impossible

To Test the patients biomarker values, a biopsy of the initial tumour is necessary. However, it is not always possible to take a biopsy from the tissue due to the location of the tumour. Not being able to take a biopsy occurs in 10% of the patients (Mehra, 2018)

Response and Biomarkers for Atezolizumab

The response rates for immunotherapy in terms of Progressive disease (PD), Stable Disease (SD), Partial Response (PR) and Complete Response (CR) are known from literature (Rosenberg et Al., 2016). The biomarkers PD-L1 expression, TCGA subtype, and Mutational Load score, correlate with the response rates. The data for response and the biomarkers are retrieved from the figure in appendix C.

Response to atezolizumab

In the table below, the response rates are given for the total population with mUC:

	Probability
Progressive Disease	0.60
Stable Disease	0.22
Partial Response	0.12
Complete Response	0.06

Table 6: Response Rates

TCGA subtype

The TCGA subtype correlates with the Response to atezolizumab. In Table 7 the probabilities for the TCGA subtype, given a certain response, are stated.

	cluster1	*cluster2*	*cluster3*	*cluster4*
PD	0.38	0.18	0.26	0.17
SD	0.48	0.28	0.05	0.19
PR	0.25	0.39	0.16	0.19
CR	0.06	0.6	0.16	0.18

Table 7: TCGA Signatures (Rosenberg et al., 2016)

PDL1 score

The PDL1 score is divided into 3 subgroups and correlates with the TCGA signature. The probabilities for the PD-L1 score, given a certain TCGA signature, are stated below.

	IC0	*IC1*	*IC23*
cluster1	0.47	0.38	0.15
cluster2	0.28	0.38	0.34
cluster3	0.11	0.21	0.68
cluster4	0.09	0.41	0.5

Table 8: PD-L1 score

ML Score

The mutational load is given in a continuous scale, and therefor in literature stated in a boxplot. In these boxplots patient are correlated with TCGA subtype, and grouped by SD/PD and PR/CR.

			Luminal				*Basal*			
	All clusters		Cluster 1		Cluster 2		Cluster 3		Cluster 4	
	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR
min	0	3	0	4	1	7	1	7	1	5
1quartile	5	10	5	11	5	11	5	12	3	7
median	7	13	7	13	9	13	8	14	5	14
2quartile	11	19	11	20	14	18	11	22	10	20
max	21	24	17	22	21	19	19	22	18	24

Table 9: TCGA boxplot data

Based on the first quartile, median and third quartile, a distribution is estimated. The box plot seems to correspond most closely with a gamma distribution. Formulas to calculate S, $\bar{X}$, Alfa and Beta are explained in appendix D. The table below gives the Alfa and Beta value for the gamma distribution.

	Luminal				*Basal*			
	Cluster 1		Cluster 2		Cluster 3		Cluster 4	
	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR
S=(q3-q1)/1,35	4.44	6.67	6.67	5.19	4.44	7.41	5.19	9.63
$\bar{X}$ *=(q1+m+q3)/3*	7.67	14.67	9.33	14.00	8.00	16.00	6.00	13.67
α = ū2 / s2	**2.98**	**4.84**	**1.96**	**7.29**	**3.24**	**4.67**	**1.34**	**2.01**
β = s2/ ū	**2.58**	**3.03**	**4.76**	**1.92**	**2.47**	**3.43**	**4.48**	**6.79**

Table 10: Alfa and Beta for TCGA distribution

Adverse events

We divided the adverse events into grade 0, grade 1/2 and grade 3/4. The probabilities for each treatment are given in the table below. The probabilities that are given are the change to an adverse event, per treatment and not per cycle.

	0	*Grade 1/2*	*Grade 3/4*	*Reference*
GemCis	0.1	0.41	0.49	(Bellmunt et al., 2009)
GemCarbo	0.2	0.31	0.49	(Rosenberg et al., 2016)
Atezolizumab	0.31	0.54	0.16	(Rosenberg et al., 2016)

Table 11: Adverse event probabilities

The average duration of the symptoms and the average duration for the admission for patients with grade 3/4 adverse events are stated below. Assumed is that grade 1 and 2 adverse events will not contribute in costs or HRQoL.

	Duration in days	*Duration in days*
Average duration symptoms Tox3/4	5	14
Average duration admission tox3/4	2.5	7

Table 12: adverse event effects

Progression free survival chemotherapy

The decisions made in the model are based on whether the patient has progression or not. In Table 13 progression free survival for each chemotherapy regimen are given. These probabilities are the change of not having progression, x months after chemotherapy treatment started. GemCis 2nd and GemCarbo 2nd, stand for the second chemotherapy treatment, which is given if progression occurred from 12 months after start of the first chemotherapy treatment.

months	*GemCis*	*GemCarbo*	*GemCis 2nd*	*GemCarbo 2nd*
3	0.85	0.7	0.75	0.6
6	0.73	0.46	0.72	0.41
9	0.38	0.28	0.35	0.23
12	0.27	0.11	0.23	0.08
15	0.22	0.06	0.18	0.03
18	0.16	0.04	0.11	0.02
21	0.11	0	0.04	0.01
24	0	0	0	0

Table 13: PFS for chemotherapy

Response atezolizumab

Because there are multiple subpopulations in the alternative path who receive atezolizumab, and literature is deficient in terms of progression free survival per subgroup, we use PFS for response groups in terms of PD, SD, PR, and CR. The average progression free survival for patients with a stable disease and patients with response are known, so those values are used in the model. Patients with progression will not continue treatment. The progression free survival per response group are stated in Table 14: PFS for Atezolizumab (Balar et al., 2017; Rosenberg et al., 2016).

months	*Complete Response*	*Partial Response*	*Stable disease*	*Progressive disease*
3	1	1	0.88	0
6	1	1	0.88	0
9	1	0.88	0.63	0
12	1	0.88	0.63	0
15	1	0.88	0.63	0
18	1	0.88	0.63	0
21	1	0.88	0.63	0
24	1	0.88	0.63	0

Table 14: PFS for Atezolizumab

For the atezolizumab responsive and stable patients, several assumptions need to be made, because literature does not provide information on follow-up longer than 24 months. For the complete responders, we assume that the cancer will not come back and those patients will have a normal life expectancy (see next section). For the partial responders and the stable disease patients, we assume a progression free survival of 5 years, during this period they will stay in follow up and undergo a CT-scan to assess the tumour. In the model no distribution is used for the assumed 5 years of follow up.

Additional life expectancy after complete response:

We want the additional life expectancy for people born in 1952, given they reach the age of 66. The additional life expectancy for these people is: **18.8 Years.** See Appendix E for calculation.

HRQoL

To calculate the QALY's we need the health related quality of life of the patients during the treatment and follow up.

HRQoL	*Chemotherapy*	*Atezolizumab*	*Reference*
Week 0	0.59	0.61	(Vaughn et al., 2017)
Average Delta Tox3/4	-0.03	-0.08	Dr. Niven Mehra
Average delta during therapy	-0.08	0.01	(Vaughn et al., 2017)
BPOC	0.25	0.25	assumption
HRQoL stable disease	-	0.65	assumption
HRQoL Partial response	-	0.7	assumption
HRQoL Complete Response	-	0.8	(CentraalBureauStatistiek, 2015)

Table 15: Health related quality of life

Costs

In the table below the costs are given that are needed in the model

Description	*Costs*	*Reference*
Treatment, medicine and follow up for GemCis Treatment per cycle	€ 3.000	(Mehra, 2018)
Treatment, medicine and follow up for GemCarbo Treatment per cycle	€ 1.000	(Mehra, 2018)
Treatment for atezolizumab per month	€ 1.000	(Mehra, 2018)
Atezolizumab medicine per month	€ 5.000	(Mehra, 2018)
CT-Scan including assessment	€ 900	(Mehra, 2018)
Biopsy	€ 600	(Mehra, 2018)
PDL1 Test	€ 300	(Mehra, 2018)
TCGA Test	€ 300	(Mehra, 2018)
Mutational load Test	€ 2.500	(Mehra, 2018)
Admission day for adverse event	€ 2.200	(CBS, 2018)
Hospital costs for best path of care per month	€ 2.500	assumption

Table 16: Costs

4.2 Output Measures

The main output measure of the model are the total costs and the QALYs. To calculate these output measures the model keeps track of a list of attributes for each patient. The values of these attributes will be written to the output table at the end of the simulation. In Table 17, all patient attributes are listed and explained.

Attribute name	*description*
PatientID	Keep track of patient ID
TimeInCT	Total months spent during chemotherapy
TimeInIT	Total months spent during immunotherapy
TimeInBPOC	Total time spent in best path of care
TimeInPR	Time for partial responders between IT treatment and BPOC
TimeInCR	Time for complete responders between IT treatment and Death
CostsCT	Costs for chemotherapy treatment and medicine
CostsIT	Costs for immunotherapy treatment and medicine
CostsBPOC	Hospital costs during best path of care
CostsAECT	Hospital costs due to adverse events (3/4) during chemotherapy
CostsAEIT	Hospital costs due to adverse events (3/4) during immunotherapy
CostbiomarkerTest (only alternative path)	Costs for testing biomarkers PDL1, ML and TCGA
CostsCTAssessment	Costs for CT scans (including assessment) during chemotherapy
CostsITAssessment	Costs for CT scans (including assessment) during immunotherapy
QALY	Total QALYs since treatment start
CTGroup	1 = cisplatin eligible 2 = cisplatin ineligible 3 = chemotherapy ineligible
ITgroup	1 = IC23 2 = IC1 ML+ 3 = IC1 ML- TCGA2 4 = IC0 ML+ TCGA2 5 = chemo ineligible 6 = biopsy impossible 7 = Total population
ITProgression	1 = Progressive disease 2 = Stable disease 3 = Partial Response 4 = Complete Response
TargetIT (only alternative path)	Yes = Immunotherapy arm No = chemotherapy arm

Table 17: patient attributes

4.3 THE SIMULATION MODEL

Here we will discuss each part of the model, starting the main frame and general choices and limitations of the model, where after the current and alternative path will be discussed, and at the end the outcome measures of the model.

4.3.1 The Mainframe

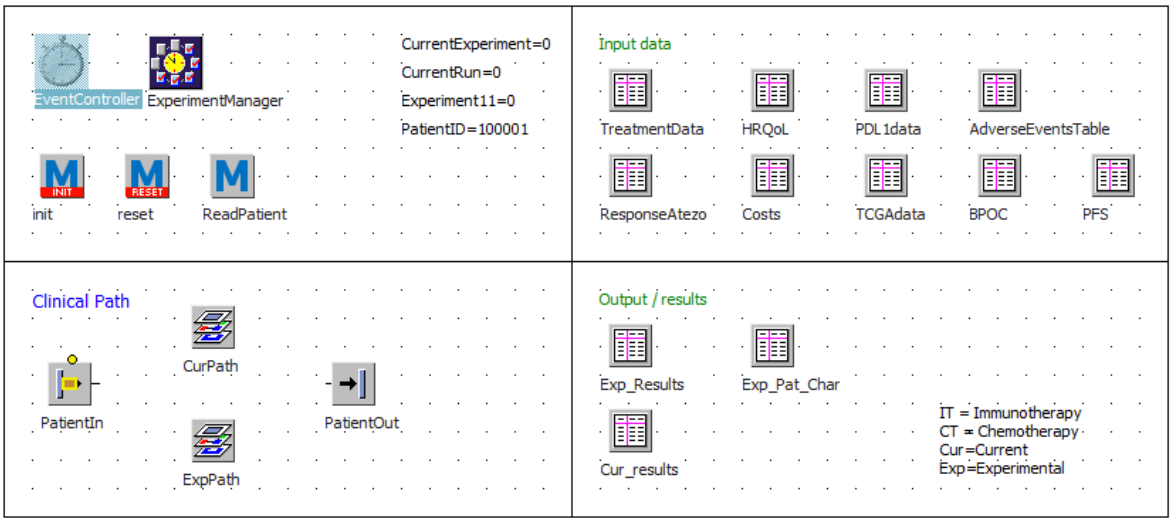

Figure 8: Mainframe

In **Fout! Verwijzingsbron niet gevonden.** of the model can be seen. On the left side of the frame the actual discrete event simulation is modelled. The clinical path consists of a source, called PatientIn, where the patients are created. Thereafter the patient will go to the Current path (CurPath), or the alternative path (ExpPath), which are sub frames with own objects. Lastly when the patient leave the model, they go to the drain, called PatientOut. All movements, including the movements in the sub frames are triggered by methods, because the next object for the patient depends on certain characteristics and response probabilities. The methods make the arrows to connect the objects unnecessary.

On the right side of the frame all the input and output tables are stated.

Ideally we want to run a simulation with patient level data, whose responses for chemotherapy and immunotherapy are known, given certain characteristics of the patient. Then we can use the model to guide the patient through the current and alternative pathway and see whether the patient is categorised correctly in the chemotherapy arm, or the immunotherapy arm. In this ideal situation we can see what percentage false negative, false positive, true negative and true positive patients the decision model gives, so we can calculate the sensitivity and specificity of the model. There after the parameters of the decision model can be adjusted to increase the sensitivity and specificity of the model.

However, we do not have patient level data for the study population and instead we need to create patients with data from literature. For these patients the true response is not known, and instead a response probability is given for each patient based on patients' characteristics. For chemotherapy the response is based on the different regimens of

chemotherapy, i.e. Gem/Cis or Gem/Carbo. For the immunotherapy group the response probabilities are based on the biomarkers PD-L1 expression, mutational load and TCGA signature.

In reality the progression of the tumour will be checked by assessing a CT-scan with the RECIST criteria, whereby a sensitivity and the specificity of the test are not 100%. In this model we assume that the classification of the tumour is 100% correct for each test.

As can be seen in the pathways for the current and alternative pathway, all the events will happen on certain moments in time, and assumed is that the state of the patient or model will not change in between those moments. Therefore, a discrete event simulation is used.

4.3.2 PatientIn

When a patient arrives in the source, the method "ReadPatient" is triggered. The main objective of this method is to give the patient certain characteristics and send the patient to the current or alternative path. Which characteristics those are, are stated below.

- Keep track of the PatientID, in order to write output data to the correct patient.
- Give the patient a Biopsy characteristics, i.e. is a biopsy possible for this patient. The model picks a random number between 0 and 1 and compares this number with the probability that a biopsy is possible. When the random number is smaller than the biopsy probability, @.biopsy=true, otherwise, @.biopsy=false.
- Give the patient a chemotherapy group in terms of; chemotherapy ineligible, cisplatin ineligible or cisplatin eligible. Again a random number between 0 and 1 is assigned to the patient, and this number is compared to the probabilities of the 3 chemotherapy groups. The code in the model will look like the following:

```
--check whether chemo/cisplatin is possible
var pChemo : real
pChemo:=z_uniform(1,0,1)//assign random nr. for pChemo to compare with probability from
table
if pChemo < TreatmentData[1,"ChemotherapyIneligible"]
    @.CTGroup:=3            // patient is chemotherapy ineligible
else
    if pChemo <
            (TreatmentData[1,"ChemotherapyIneligible"]+TreatmentData[1,"CisplatinIneligible"])
            @.CTGroup:=2  // patient is cisplatin ineligible
    else
            @.CTgroup:=1   // patient is cisplatin eligible
    end
end
```

- Give the patient a random number for the probability on side effects for both chemotherapy and immunotherapy. These random numbers will later on be compared to the adverse event probabilities.
- Give the patient an IT Progression number; 0=PD, 1=SD, 2=PR, and 3=CR.

- Give the patient a random number between 0 and 1 for the TCGA probability. With this number a TCGA signature is assigned to the patient, given a certain IT progression
- Give the patient a PD-L1 expression score in terms of IC0, IC1 and IC2/3. Again, at first a random number is assigned, which is compared to the probabilities from literature for the different IC groups, given a certain TCGA signature.
- The mutational load is given by a calculated gamma distribution. Depending on the TCGA signature and response, the gamma distribution is calculated.
- At the end the patient will be duplicated so that each patient will undergo the alternative path and the current path for comparison. The patient will be duplicated so the current path and the alternative path will have the exact same patient group and so the comparison will be based on the same group.

4.3.3 The Current Path.

In Figure 9: The Current Path, you can see what the current path looks like in the simulation model.

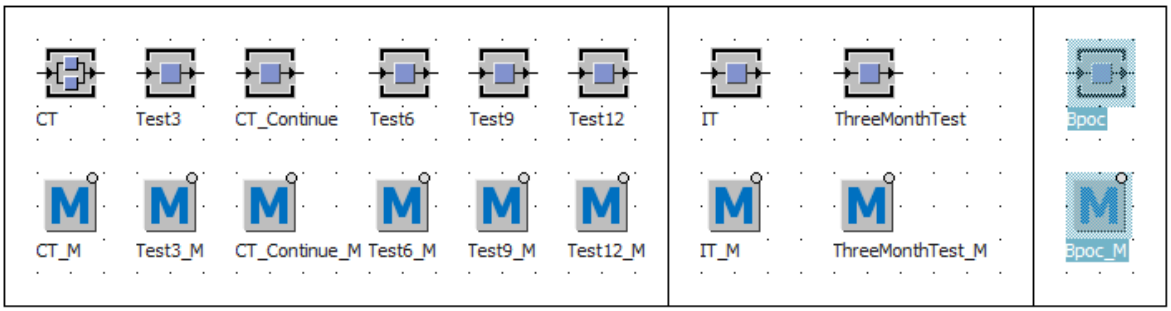

Figure 9: The Current Path

Object CT

When a patient enters the current pathway, the patient is already diagnosed with mUC, and the chemotherapy group the patient belongs in is known. For patients in chemotherapy group 3, i.e. no chemotherapy is possible, the patients are directly send to the object IT (Immunotherapy). For the patients with chemotherapy group 1 (cisplatin eligible) and group 2 (cisplatin ineligible), the corresponding chemotherapy treatment is given.

The random number for the adverse events that is assigned in “ReadPatient” is now compared to adverse event probability in the input table. The patient will be categorized as AdverseEventCT0, AdverseEventCT12 or AdversEventCT34, where the numbers stand for the grade of the adverse event. When the patients is categorized as grade 3/4, the corresponding costs and reduction in quality of life, is written to the patients characteristics. The costs for the chemotherapy treatment for each patient are written to the patient characteristics as well. These costs consist of the treatment and medicine costs for the 4 treatment cycles in the first three months. Afterwards the patient will be sent to the 3-month-test.

Object Test3

In Test3 the model checks whether the patients responds to the chemotherapy after the first 3 months of the treatment. The method checks the chemotherapy group (GemCis / GemCarbo) and whether this is the first or second chemotherapy treatment for the patient. In the PFS table the random number for chemotherapy response will be compared with the PFS probability for three months in the corresponding column. If the patient does not have progression, he will move to CT_Continue. If the patient does have progression, the chemotherapy treatment will be aborted and the patient will be sent to the object IT, to receive immunotherapy in the second-line treatment.

Object CT_Continue.

The costs for treatment and medicine for the 5^{th} and 6^{th} chemotherapy cycle are written to the patient's data. Then the patient will be sent to the 6-month test.

Object Test6

The method that is triggered by object Test6, tests whether the patient has progression after 6 months, given the chemotherapy treatment he receives. When progression has occurred, the patient will be sent to the object IT. When no progression did occur the patient will stay in follow up and will be sent to the object Test9.

Object Test9

The method that is triggered by object Test9, tests whether the patient has progression after 9 months, given the chemotherapy treatment he receives. When progression has occurred, the patient will be sent to the object IT. When no progression did occur the patient will stay in follow up and will be sent to the object Test12.

Object Test12

If progression occurs after 12 months, the patient will receive another chemotherapy treatment, under the condition that the current chemotherapy treatment is the first. Since progression always occurs within 24 months, Test12 will test the patient on months 12, 15, 18, 21 and 24.

In the method a for loop is initiated to loop the patient through the test on month 12 (i=4) till the test on month 24 (i=8). At the beginning of each test the method will keep track of the duration that the patient is in chemotherapy. Then the method will check whether the patient has progression or not. When the patient has no progression, the loop will continue to the next test. When the patient has progression, and the current treatment number is 1, he will be sent back to CT to receive a second chemotherapy treatment. When the patient has progression while having his second chemotherapy treatment, he will be sent to the object IT.

Object IT

The method has to decide whether the patient will get adverse events, and when he does which grade that adverse event will be. A random number between 0 and 1 will be generated to compare it with the data in the AdverseEvent table. Then the patient will be categorized as; no adverse events, adverse event grade 1/2, or adverse event 3/4. When

a patient will have adverse events, the corresponding costs and reduction in quality of life, is written to the patients characteristics.

At last the patient will be sent to the object ThreeMonthTest.

Object ThreeMonthTest

When the patient is categorized as progressive disease, it will be directly send to the best path of care, because other treatment options are not available. The costs for the first three months of immunotherapy will be written to the patient's data.

For the other patients, the patient will loop through the months 3 to 24, with steps of 3 months. Every 3 months a new test will be performed to check whether the patient has progression and the costs for the treatment are written to the patient's data. As long as there is no progression, the treatment with atezolizumab will continue. When progression occurs, the patient will be sent to the BPOC. When patients have not shown progression within 24 months, assumed is that they stay in follow up for another 3 years. During these years no atezolizumab is given anymore. For patients that are categorized as complete responders the follow up is not necessary anymore and assumed is a normal additional life expectancy (see 4.3.1 inputs).

Object BPOC

When the patient arrives in the best path of care, the average duration of BPOC and the corresponding QALY's and costs are written to the patient data. There after the output table will be filled with the patient's data.

4.3.4 The alternative path

In the alternative path the patient will be directed Immunotherapy arm or the chemotherapy arm by help of a clinical decision algorithm as seen in the following figure, where ArmITCT represents the Immunotherapy arm, and ArmCT represents the chemotherapy arm.

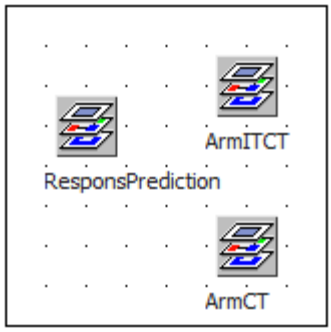

Figure 10: alternative Path

Response Prediction

In this object the patient goes through a stepwise method, in which the patient is targeted to immunotherapy or chemotherapy in the first line. In the table below the different groups of patients that will receive immunotherapy are listed. The patients that cannot be categorized in one of the 6 ITgroups below, will be redirected to the Chemotherapy arm.

Group	*PD-L1 expression*	*Mutational Load*	*TCGA subtype*
1	IC23	Non relevant	Non relevant
2	IC1	>11	Non relevant
3	IC1	<11	Subtype 2
4	IC0	>11	Subtype 2
5	Chemotherapy ineligible		
6	Biopsy not possible		

Table 18: ITgroups

During the method the costs for the biomarker test are recorded.

Immunotherapy arm

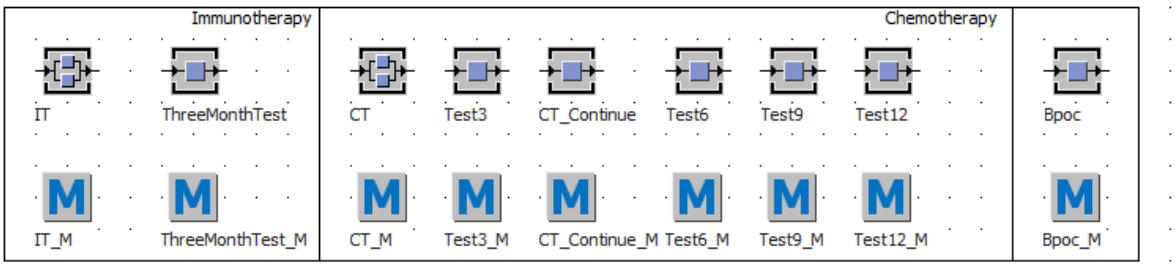

Figure 11: alternative Path ArmITCT

The patients who arrive at object IT do all have a certain ITgroup from 1 to 6, which corresponds to characteristics of the patient (see Table 18), and response in terms of PD,

SD, PR, and CR are known. Next, the effects of adverse events in terms of costs and QALYs are kept track of, the same way as in the current pathway, and the patient will be sent to the object ThreeMonthTest.

The rest of the methods function is mostly the same as they do in the current pathway, except for the object they are being sent to after having progression.

Chemotherapy arm

In Figure 12, model wise pathway for the chemotherapy arm is shown. As can be seen no immunotherapy is given for patients in this arm, because they are most likely to not respond to atezolizumab. The methods in the frame are the same as in the current pathway, except for the object they are being sent to after having progression.

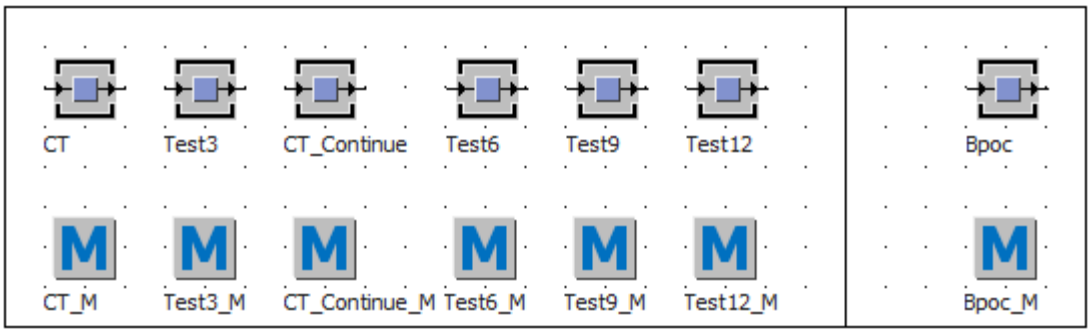

Figure 12: ALTERNATIVE PATH ARMCT

4.3.5 Patient Out

Once the patient has left the BPOC the patient is deceased, and leaves the model through the drain: PatientOut. When the last patient of the experiment left the model through the drain, the experiment is done.

4.4 DATA ANALYSIS

To analyse the results, multiple calculation will be made. First of all, the power of the clinical decision algorithm will be tested, by testing how many patients, per patient group will be targeted to immunotherapy, and what the sensitivity, specificity, Positive predictive value, and negative predictive value are. Then the cost effectiveness of both the current pathway and the alternative pathway, including the incremental cost effectiveness ratio are discussed. Thereafter the cost-effectiveness is tested for multiple hypothetical sensitivities and specificities of the clinical decision algorithm, as well for different response rates for immunotherapy in the firs-line treatment. At the end a sensitivity analysis is performed, of which the method is explained in the next section.

4.4.1 Sensitivity analysis

Since a lot uncertainty exists around the parameters that are used as input in the model, a sensitivity analysis will be performed. Hereby we can see how the uncertainty in the output can be appointed to the different input parameters. In our sensitivity analysis we will change the input parameters with a decrease of 20% and an increase of 20%. The parameters that are not taken into account are the progression free survival rates for immunotherapy and chemotherapy, since those are known from literature and changing those input parameters would give a distorted view of reality. Also the input parameters on the response rates and biomarker values are not taken into account, since they correlate with each other. Changing one biomarker would result in the change of multiple biomarkers, and therefore, the experiment outcomes will be the result of the change of multiple biomarkers, instead of one. The values of all the other input parameters are listed in the table below.

Experiment	*Base Case*	*20%*	*-20%*	*
Biopsy Impossible	10%	12%	8%	
Chemo ineligible	5%	6%	4%	
Cisplatin ineligible	40%	48%	32%	
GemCis costs	€ 3.000	€ 3.600	€ 2.400	
GemCarbo costs	€ 1.000	€ 1.200	€ 800	
Atezolizumab treatment costs	€ 1.000	€ 1.200	€ 800	
Atezolizumab medicine costs	€ 5.000	€ 6.000	€ 4.000	Extra experiment with €10.000
BPOC Costs	€ 2.300	€ 2.760	€ 1.840	
CTS can Costs	€ 900	€ 1.080	€ 720	
Biopsy Costs	€ 300	€ 360	€ 240	
PDL1 test Costs	€ 600	€ 720	€ 480	
TCGA test Costs	€ 300	€ 360	€ 240	
ML test costs	€ 2.500	€ 3.000	€ 2.000	
Admission Day costs	€ 2.000	€ 2.400	€ 1.600	
Admission Day AE costs	€ 1.800	€ 2.160	€ 1.440	
BPOC length	4,30	5,16	3,44	In months
BPOC HRQoL	0,20	0,24	0,16	
Baseline HRQoL CT	0,59	0,71	0,47	
CT HRQoL Tox3/4	-0,03	-0,04	-0,02	
CT Duration admission AE 3/4	2,50	3,00	2,00	in days
CT HRQoL during therapy	-0,08	-0,10	-0,06	
CT Duration symptoms AE 3/4 +	5,00	6,00	4,00	in days
Baseline HRQoL IT	0,61	0,73	0,49	
IT HRQoL AE 3/4	-0,08	-0,10	-0,06	
IT Duration admission AE 3/4	7,00	8,40	5,60	in days
IT HRQoL during therapy	0,01	0,00	0,02	manual adjustment
IT Duration symptoms AE 3/4	14,00	16,80	11,20	in days
IT HRQoL Complete response	0,80	0,96	0,64	
Duration of complete response till death	216,00	259,20	172,80	In months
HRQoL Partial response	0,70	0,84	0,56	
Duration of Partial disease till BPOC	36,00	43,20	28,80	In months
AE GemCis 34 probability	0,31	0,372	0,25	
AE GemCarbo 34 probability	0,54	0,648	0,43	
AE Atezo 34 probability	0,16	0,192	0,13	

Figure 13: sensitivity analysis input parameters

In the model, a table is made for the input of the experiments. In each experiment, only one parameter is adjusted. When the patient is done in the simulation, the output parameters are written into two tables: expTotal, where all output parameters are stated,

and a table ExpSum, where only the average costs and QALYs per patient per experiment are stated. Outcome measures that are used for the sensitivity analysis are: incremental costs, incremental QALYs, incremental costs per QALY, and Net monetary benefit. The net monetary benefit (NMB). The NMB is calculated by multiplying the incremental benefit with the willingness to pay, minus the incremental costs (YHEC, 2016).

4.5 NUMBER OF PATIENTS

To get stable output data, the model has to run for a certain number of patients, otherwise the model returns different output measures (average cost/QALY per patient) for different random number seeds. When the number of patients is high enough, the stochastic uncertainty will be that small that outcome measures will be approximately the same for different random number seed values. We use the principle of law to see when the curve "flattens". In the figures in appendix F we can see that the curve has flattened at around 50.000 patients for the main outcome measures; total costs per patient, total QALY's per patient, and costs per QALY.

5 RESULTS

In this chapter we will analyse and discuss the results from the simulation model to answer the main question of this thesis.

What is the expected health economic impact of selecting for responsive patients for immunotherapy in the first line setting in patients with metastatic urothelial carcinoma using a combination of biomarkers, in comparison to standard therapy that consists of treatment of all comers with chemotherapy in the first-line treatment followed by immunotherapy in the second line?"

In the first section, the response rates for the current and alternative path will be discussed. Then the specificity and sensitivity of the clinical decision algorithm will be discussed where after it is about the cost effectiveness of both paths. At the end the results of the sensitivity analysis will be discussed.

5.1 PATIENTS PER IT-GROUP IN THE ALTERNATIVE PATH

In the alternative path, patients not likely to not respond to immunotherapy are withheld this treatment, reducing morbidity and costs. With the parameters that are used in the clinical decision algorithm, immunotherapeutic treatment will be withheld for 37% of the patients. For 49% of the patients, immunotherapy is targeted in the first line based on their biomarkers, and 14% of the patients receive immunotherapy because chemotherapy or a biopsy is not possible. In the figure below, an overview is given of the distribution of patients per group.

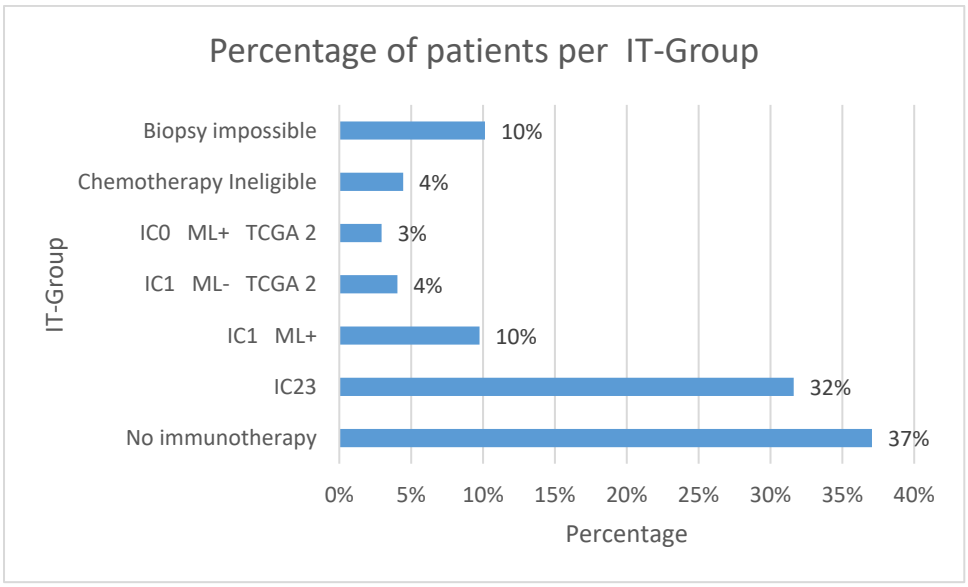

Figure 14: percentage of patients per IT Group

5.2 RESPONSE TO IMMUNOTHERAPY

The response rates to immunotherapy are determinative for the cost effectiveness of the alternative path in comparison to the current path. The more accurate the clinical decision algorithm is, the higher the percentages for response and stable disease are. In the table

below the response rates are stated for the current and alternative path, given that the patient received immunotherapy. In the column "Current Path, the response rates are given for the total population in the current path. In the column "Alternative Path", the response rates are solely given for patients who received immunotherapy based on their biomarkers in the alternative path (i.e. the patients ineligible for chemotherapy and biopsy are excluded). If include the chemotherapy and biopsy ineligible patients, with the current input parameters, the same percentages would show up. This is due to the fact that the biopsy and chemotherapy ineligible patients have the same response probabilities as the rest of the patients.

Response status Immunotherapy	*Current path – All patients*	*Alternative path – IT-arm*
Progressive disease	60%	55%
stable disease	22%	21%
Partial Response	12%	15%
Complete Response	6%	9%

table 19: response rates current vs. alternative path

We can see that the percentages for patients with complete and partial response, for immunotherapy in the alternative path, are slightly higher than in the current path. The clinical decision algorithm should target patients with a higher probability for response to the immunotherapy arm. The results in table 19 show that the patients in the immunotherapy arm indeed have a higher response probability, however in the alternative path, there is still a certain amount of people who are withheld from treatment with atezolizumab, who should have responded. We calculate that percentage in the next section.

5.3 SENSITIVITY AND SPECIFICITY OF THE MODEL

To calculate the sensitivity and specificity of the clinical decision algorithm we make use of the following table:

		Response in reality	
		Responsive	Progressive
Predicted response according to clinical decision algorithm	Immunotherapy arm	A=True positive	B=False Positive
	Chemotherapy Arm	C=False Negative	D=True negative

Table 20: sensitivity and specificity

For the immunotherapy arm, we only include the patients who received immunotherapy based on their biomarkers.

From published data we extracted the number of patients classified as A, B, C and D. For the responsive patients, we defined all patients with a stable disease, partial response, and complete response at 52 weeks.

		Response in reality	
		Responsive	Progressive
Predicted response according to clinical decision algorithm	Immunotherapy arm	10745	13433
	Chemotherapy Arm	6320	12210

Table 21: sensitivity and specificity results

Based on the numbers in the table above we can calculate the sensitivity, specificity, Positive Predictive Value (PVV) and Negative Predictive Value (NPV) of the clinical decision algorithm:

$$Sensitivity = \frac{a}{a+c} = \frac{10745}{10745+6320} = 0.63$$

This means that 63 percent of the responding patients will indeed receive immunotherapy. For the other 37 percent of patients, whom would have responded in reality, will have their immunotherapy withheld.

$$Specificity = \frac{d}{d+b} = \frac{12210}{12210+13433} = 0.47$$

This means that 47 percent of the patients who will not respond in reality, indeed will not receive immunotherapy. I.e. 53 percent of the patients who do not respond, will receive immunotherapy. When the goal of the model is to prevent overtreatment, the specificity should be as high as possible; when the specificity is equal to 1, none of the patients who will not respond in reality, would receive immunotherapy.

Positive predictive value

$$PPV = \frac{a}{a+b} = \frac{10745}{10745+13433} = 0.44$$

This means that in 44% of the cases that the algorithm predicted response, the patient indeed had response.

Negative predictive value

$$NPV = \frac{d}{c+d} = \frac{12210}{6320+12210} = 0.66$$

This means that in 66% of the cases that the algorithm predicted no-response, the patient indeed had no-response.

As the results in this section show, the performance of the clinical decision algorithm needs much further improvement, as the current predictive biomarkers in urothelial carcinoma limit response prediction. If improved evidence on the current biomarkers combinations, or when new biomarkers show up in the future, adaptation of the algorithm in the

alternative path will result in an improved sensitivity and specificity. In section 5.6 we modelled how an improvement in predictive biomarkers may increase the sensitivity and specificity of the model, to study the influence of a performance of the decision model on the effect of cost-effectiveness.

5.4 THE COST EFFECTIVENESS

In the incremental Cost Effectiveness Ratio (ICER) we evaluate what the additional costs per QALY are. In the table below, the average costs and QALYs are given for the current pathway and the alternative pathway.

	Costs Chemotherapy	*Costs Immunotherapy*	*Total Costs per patient*	*QALY per patient*	*CostsPerQaly*
Current Path	€ 15.110	€ 58.306	€ 92.984	2,36	€ 39.437
alternative	€ 15.081	€ 41.243	€ 75.729	2,08	€ 36.355
Incremental	€ -29	€ -17.063	€ -17.255	-0,28	€ -3.083

Table 22: Results costs and QALYs

As we can see in the table, total chemotherapy costs remain comparable between current and alternative path, with lower total costs per patient in the alternative path, lower QALY per patient, and lower costs per QALY.

The alternative path saves costs by filtering out patients who are likely to not respond to immunotherapy. As can be seen in the table, the total cost per patient will decrease with €17.255 euro, from €92.984 to €75.729. Those savings can be explained by the fact that a part of the patients will not receive immunotherapy based on their biomarker values (37%). Those savings are higher than the costs for testing the biomarkers.

In the alternative path, the total QALYS per patient decrease with 0.28, from 2.36 to 2.08. This decrease in total QALYs is due to the poor performance of the algorithm, particularly the PPV. There is a high proportion of “false negatives” in the model whom are responsive patients, but will not receive immunotherapy due to the “bad” biomarker values. When the quality of the biomarker within the model improves, the algorithm and patient stratification will improve, with direct consequence that the QALY will increase above the current path.

In addition, our current model is underrepresenting the QALY gain for targeting patients with first-line immunotherapy. We have not included any QALY gain for the patients who are selected for immunotherapy in first versus second line, since the response probabilities for the second-line treatment are used for the first-line treatment, due to lack of clinical study data at time of this thesis. In reality the response probabilities for the first-line treatment are probably higher, and therefore, patients who are selected for immunotherapy will benefit in terms of QALYs. In section 5.6 we use hypothetical increased response rates for the first line treatment with atezolizumab.

Based on the incremental costs and the incremental QALYs the ICER is:

$$\text{ICER} = \frac{€\ 92.984\ -\ €\ 75.729}{2{,}36\ -\ 2{,}08} = €61.625\ per\ QALY$$

The ICER value above, are the total savings per lost QALY.

In **Fout! Verwijzingsbron niet gevonden.**, the result can be seen in an ICER-plot, together with a willingness to pay (WTP) of €24.500 (Bobinac, Van Exel, Rutten, & Brouwer, 2010) ,

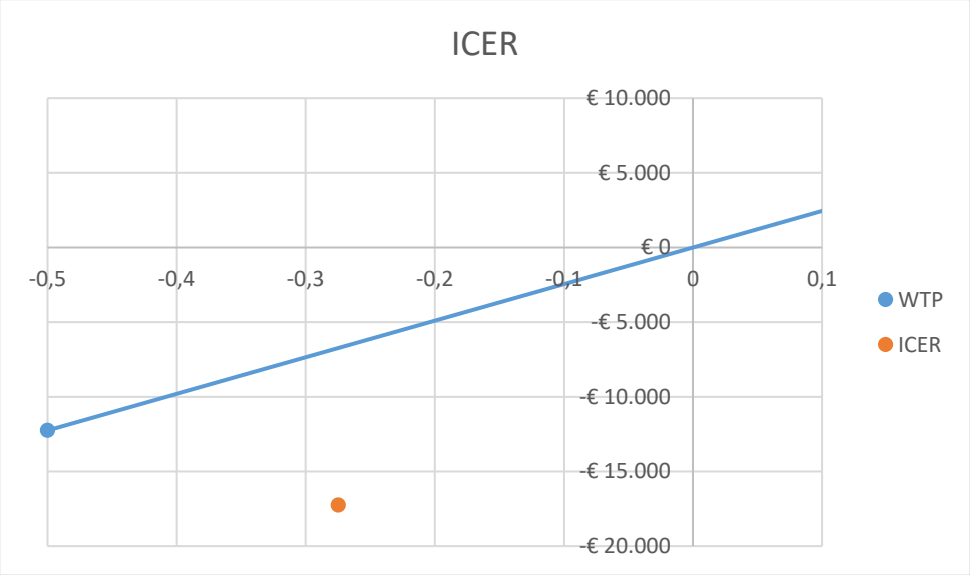

Figure 15: ICER Plot

As we can see in **Fout! Verwijzingsbron niet gevonden.**, both the incremental costs and incremental QALYs decrease. The loss in QALYs is can be explained by the fact that we used the same response probabilities for immunotherapy in the first line, as in the second-line treatment. Expected is that the true response probabilities for immunotherapy in the first line will be higher, since the patient's condition is not deteriorated, and the tumor load is not increased. When data would have been available for response probabilities for immunotherapy in the first line, we can expect that there is QALY gain for patients who receive immunotherapy in the first line. The incremental costs did decrease as well. This can be explained to the patients who did not receive immunotherapy, and thus, saved costs.

As can be seen in the ICER plot above, the result is beneath the WTP line, which means that the savings per lost QALY are higher than the amount of money that we want to pay for one QALY. However a QALY loss of 0.28 to an initial QALY of 2.36 is high.

In the previous section we have already discussed that the sensitivity and specificity are low. When in the future, better biomarkers become available, the sensitivity and specificity will probably increase. In the next section the incremental costs and QALYs, for different sensitivities and specificities of a hypothetical prediction model are discussed.

5.5 HYPOTHETICAL SENSITIVITY & SPECIFICITY

When better biomarkers become available in the future, the power of the clinical decision algorithm would probably increase. In the table below the results are stated for different sensitivities and specificities. We included also a run with a sensitivity and specificity of 100%, however this is not feasible in reality.

		Cost CT	*Cost IT*	*TotalCost per patient*	*QALY per patient*	*costs/QALY*
	Current Pathway	€ 15.110	€ 58.306	€ 92.984	2,36	€ 39.437
Sens. 85% - Spec. 90%	Alternative Pathway	€ 15.080	€ 42.901	€ 75.649	2,13	€ 35.582
	Incremental	**€ -30**	**€ -15.406**	**€ -17.335**	**-0,23**	**€ -3.855**
Sens. 90% - Spec. 95%	alternative pathway	€ 15.118	€ 44.771	€ 77.778	2,21	€ 35.203
	Incremental	**€ 8**	**€ -13.535**	**€ -15.205**	**-0,15**	**€ -4.235**
Sens. 100% - Spec. 100%	Alternative Pathway	€ 15.090	€ 48.173	€ 81.541	2,38	€ 34.326
	Incremental	**€ -20**	**€ -10.133**	**€ -11.442**	**0,02**	**€ -5.112**

Table 23: hypothetical sensitivity and specificity results

Again the results are plotted in an ICER-Plot as can be seen in **Fout! Verwijzingsbron niet gevonden.**.

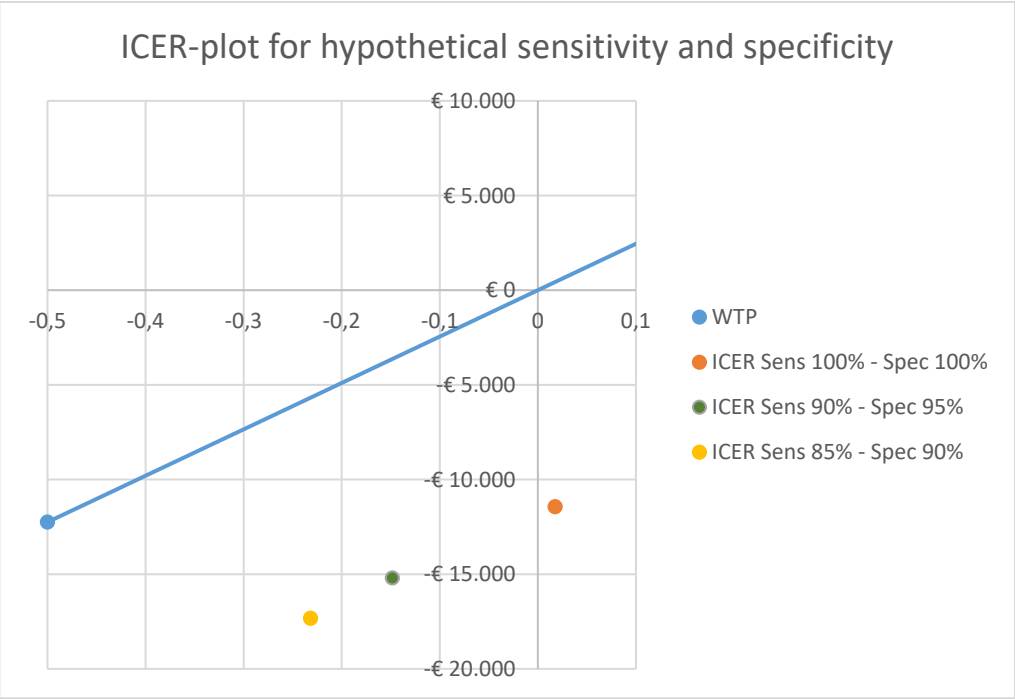

Figure 16: ICER plot hypothetical sensitivity and specificity

In the ICER plot we can see that the higher the sensitivity and specificity are, the higher the QALYs are per patient. The average savings per patient decrease as well with a higher sensitivity and specificity, which means that the costs increase. This can be declared by the fact that the patients who do respond, and who do receive immunotherapy will cost the most, since they receive immunotherapy for a maximum of 24 months. With a sensitivity of 100% all the responders will receive immunotherapy and costs increase. The specificity of 100% should cause a decrease of costs, however those savings are the cost of atezolizumab for 3 months. I.e. the savings of the high specificity cannot weigh up to the increase of cost of the high sensitivity.

5.6 HIGHER RESPONSE RATES IN THE FIRST-LINE TREATMENT WITH ATEZOLIZUMAB.

As stated before, due to lack of supporting data at present, no QALY gain is gained when immunotherapy is given in the first line, compared to immunotherapy in the second line, since the same response probabilities are used. In this section we modelled an increase in the response probability for Atezolizumab in the first line with 10%, 20% and 30%. I.e. The probability of a progressive disease decreases with 10/20/30%, and the probability of a complete response, partial response and stable disease, increase with 10/20/30% to ratio. The response probabilities are given in the table below:

	PD	*SD*	*PR*	*CR*
Base Case	0,600	0,220	0,120	0,060
Response +10%	0,540	0,253	0,138	0,069
Response +20%	0,480	0,286	0,156	0,078
Response +30%	0,420	0,319	0,174	0,087

Table 24: Response Rates IT first line

The results in terms of Costs and QALYS are listed in **Fout! Verwijzingsbron niet gevonden.**.

		Cost CT	*Cost IT*	*Total Cost per patient*	*QALY per patient*	*costs/qaly*
	Current Pathway	€ 15.110	€ 58.306	€ 92.984	2,36	€ 39.437
Response +10%	Alternative Pathway	€ 15.103	€ 45.735	€ 80.737	2,30	€ 35.104
	Incremental	**€ -7**	**€ -12.571**	**€ -12.247**	**-0,06**	**€ -4.333**
Response +20%	alternative pathway	€ 15.106	€ 49.436	€ 84.821	2,51	€ 33.860
	Incremental	**€ -4**	**€ -8.871**	**€ -8.162**	**0,15**	**€ -5.577**
Response +30%	Alternative Pathway	€ 15.114	€ 52.964	€ 88.818	2,59	€ 34.295
	Incremental	**€ 4**	**€ -5.343**	**€ -4.166**	**0,23**	**€ -5.142**

Table 25: Results adjusted Response rates IT

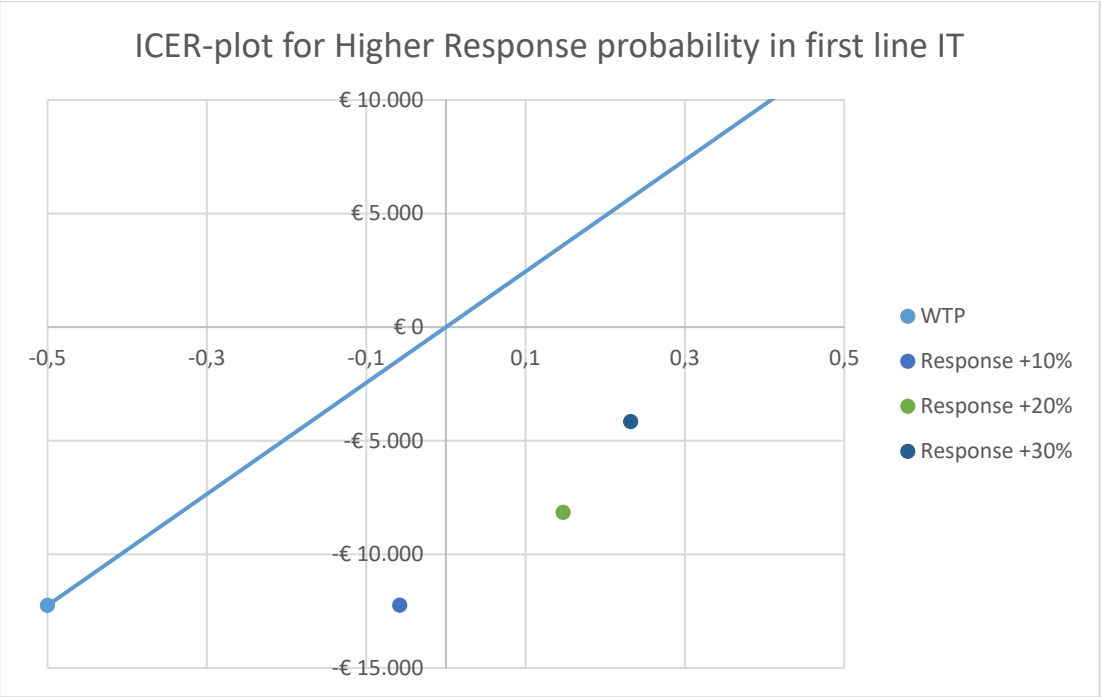

Figure 17: ICER plot hypothetical Response probabilities

In the ICER plot we can see that the higher the response rates are, the higher the QALYs are per patient, which is logical because more patients benefit from the immunotherapy. The average savings per patient decrease as well with a higher response rate, which means that the costs increase. This can be declared by the fact that the responders receive immunotherapy for a maximum of 24 months, where the non-responders receive immunotherapy for 3 months.

With an increased response rate of 10% we can see that the QALYs of targeting immunotherapy in the first line still decrease. This means that the benefit of giving immunotherapy in the first line for patients with positive biomarkers, cannot weigh up to the low sensitivity of the of the clinical decision model.

However, if the response rates for immunotherapy are 20% or 30% higher than the response rates in the second-line treatment with immunotherapy, we see an increase in QALYs, and a decrease in costs. So if in reality the response rates for immunotherapy in the first-line treatment are indeed at least 20% higher than the response rates in the second-line treatment, we can say that the cost effectiveness of targeting immunotherapy in the first line is higher, compared to giving chemotherapy in the first line, and immunotherapy in the second-line for all comers.

5.7 SENSITIVITY ANALYSIS

In the base-case scenario, multiple assumptions have been made on the input parameters. Therefore, it the results of the simulation model may not entirely reflect the results in reality. To identify which input parameters relatively most influence on the outcome, and thus may bias results the most, a sensitivity analysis is performed. As stated before in the method section, the input parameters on progression free survival and response rates for immunotherapy are not taken into account. For all the other input parameters (34), an experiment is performed with an increase and decrease of 20%, which resulted in a total of 69 experiments (including the base-case scenario).

In this sensitivity analysis the following outcome measures are included: incremental costs, incremental QALYs, incremental costs per QALY, and the net monetary benefit (NMB). For each outcome measure a tornado diagram is made for the 10 most important input parameters. The complete tornado diagrams can be seen in appendix G.

5.7.1 Incremental net monetary benefit

The net monetary benefit (NMB) is the most important outcome measure, since three important factors are taken into account; the costs, the QALYs, and the willingness to pay. A higher incremental net monetary benefit, means a better result for the alternative pathway. In the figure below the 10 most important parameters can be seen for the NBM.

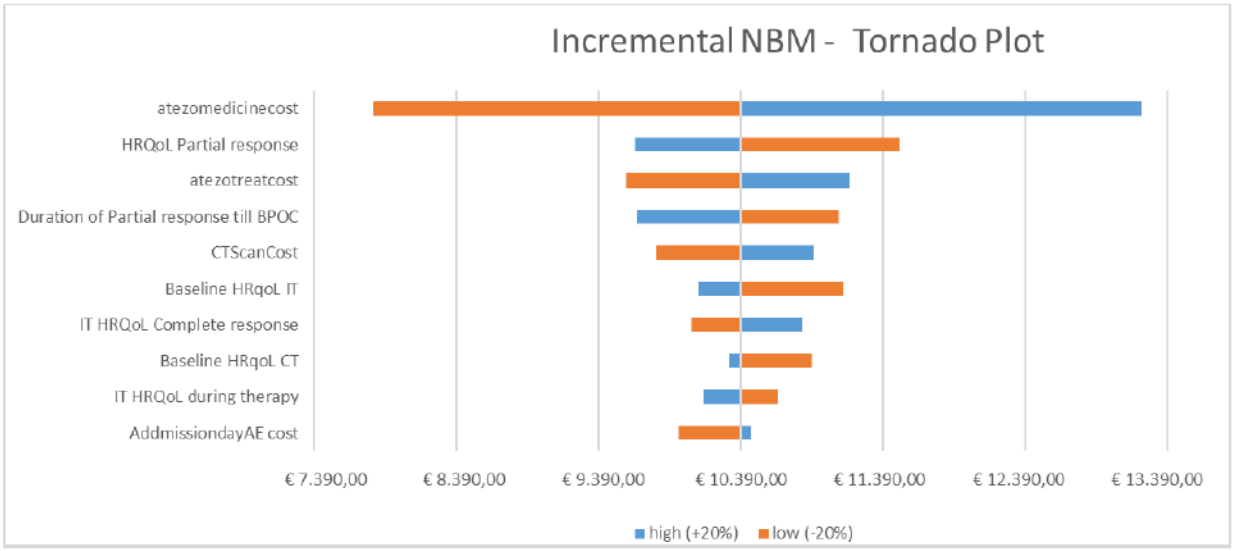

Figure 18: summary tornado plot NBM

As can be seen in the plot, the cost for the atezolizumab is the input parameter that has the most influence on the outcome. When the costs for atezolizumab increase with 20%, the incremental NMB increases with almost €3000 per patient. This can be explained by the fact that an increase in costs for atezolizumab will affect the current pathway the most, since all the patients are treated with atezolizumab. In the alternative pathway atezolizumab is given to the patients with a higher response probability, so the costs per patients are lower. The costs of atezolizumab does not affect the QALYs. An increase in atezolizumab costs, and a stable QALY and willingness to pay, result in a higher net

monetary benefit. A similar result is the case for the costs of the atezolizumab treatment costs.

The increase of the HRQoL for partial responders, and the duration of the partial response will cause an increase in NMB. In the current pathway, all patients receive atezolizumab and therefor the QALY's will increase more in the current pathway then in the alternative pathway. With no change in costs, the net monetary benefit will therefore decrease, for a higher HRQoL. The same counts for the baseline HRQoL of IT, and the HRQoL during IT treatment.

The alternative path benefits the most from an increase in CT scan costs, since there is a higher percentage of patients in the alternative path with a complete response. These patients will have no CT scans to assess the tumor after 24 months of treatment. Therefore the incremental costs for the alternative path are lower when comparing the alternative pathway to the current pathway.

The increase of costs for an adverse event admission day will result also in a higher incremental net monetary benefit, since more patients will receive immunotherapy in the current pathway compared to the alternative pathway.

5.7.2 Incremental costs per QALY

The next outcome measure Are the costs per QALY, which is strongly correlated with the net monetary benefit, since the difference in costs and QALYs are the same for the incremental costs per QALY and the incremental net monetary benefit. The difference is that the results in the table below are not compensated for the willingness to pay. In the table below, a lower incremental costs per QALY means a better result for the alternative pathway

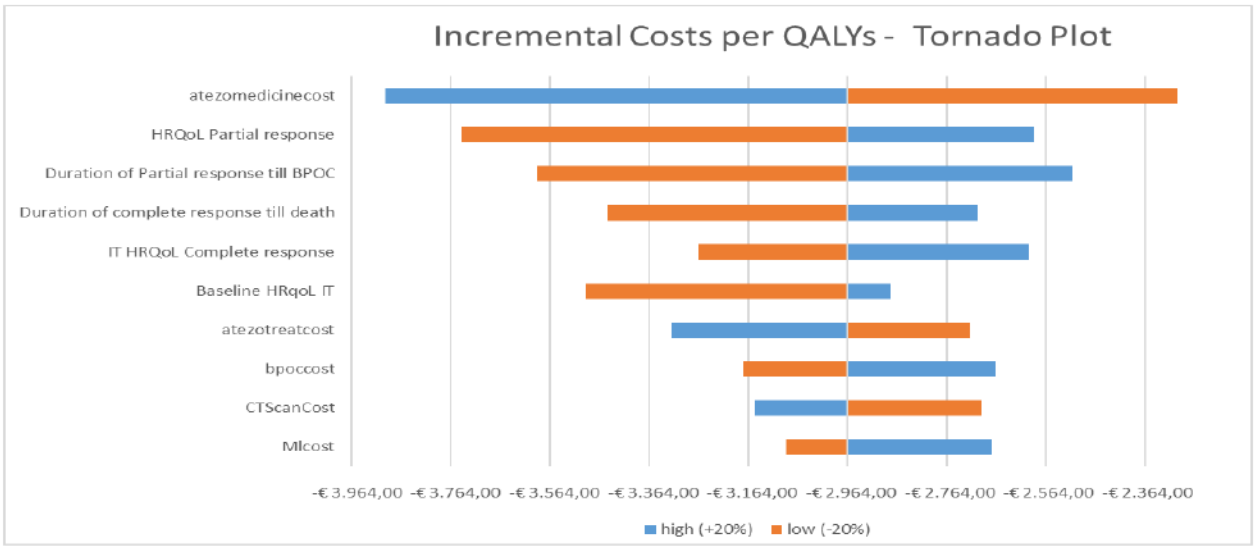

Figure 19: summary tornado plot costs per QALY

As can be seen in **Fout! Verwijzingsbron niet gevonden.**, the input parameter costs of atezolizumab, affects the incremental Costs per QALY the most. The increase of cost for atezolizumab, as well as the increase of cost for the treatment with atezolizumab and costs

for a CT scan are in favour of the alternative pathway, since the percentage of patients treated with atezolizumab is lower in the alternative pathway. In the current pathway all patients receive immunotherapy, and therefore higher costs will result in a higher raise in costs for the current pathway, compared to the alternative pathway.

The opposite is the case with the HRQoL scores that are related to immunotherapy. Since all patients receive immunotherapy, the highest amount of QALY's is reached (omitted the adverse events). So the alternative path has a disadvantage when the HRQoL, related to atezolizumab, increases.

Higher costs for a biopsy and mutational load result in a higher incremental cost per QALY, since these cost are only the case in the alternative pathway.

5.7.3 Incremental costs

In the figure below, the results are given for the incremental costs. A lower result, means a better outcome for the alternative path, since the savings are higher.

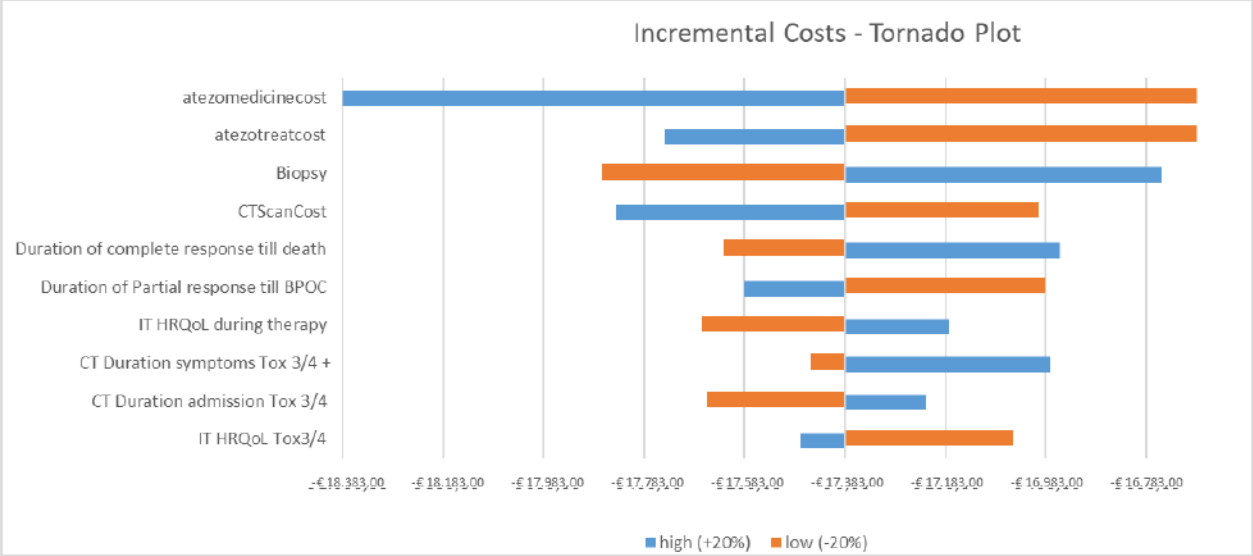

Figure 20: summary tornado plot costs

Again, the adjustment of the atezolizumab medicine costs, affects the outcome the most. An increase in costs that are related to immunotherapy treatment, will lead to a cost savings in the alternative path, since not all patients receive immunotherapy. An increase of the biopsy costs, causes an increase in incremental costs, since these costs are only made in the alternative pathway.

Increase or decrease in incremental costs as a result of an adjustment of the following input parameters are illogical, based on the model:

The increase of the duration of admission days for grade 3/4 adverse event will lead to an increase of incremental costs. This is illogical since in the current pathway all the patients receive chemotherapy, and in the alternative path not. A decrease of incremental costs is therefore the expected outcome for an increase in adverse event duration.

Duration of complete response till death: no costs are made during the period from complete response till death. Therefore it is illogical that the incremental costs increase or decrease.

IT HRQoL during therapy and adverse events: no costs are related to the HRQoL, and HRQoL does not affect other outcomes or decisions, therefore it is illogical that the incremental costs increase or decrease.

5.7.4 Incremental QALYs

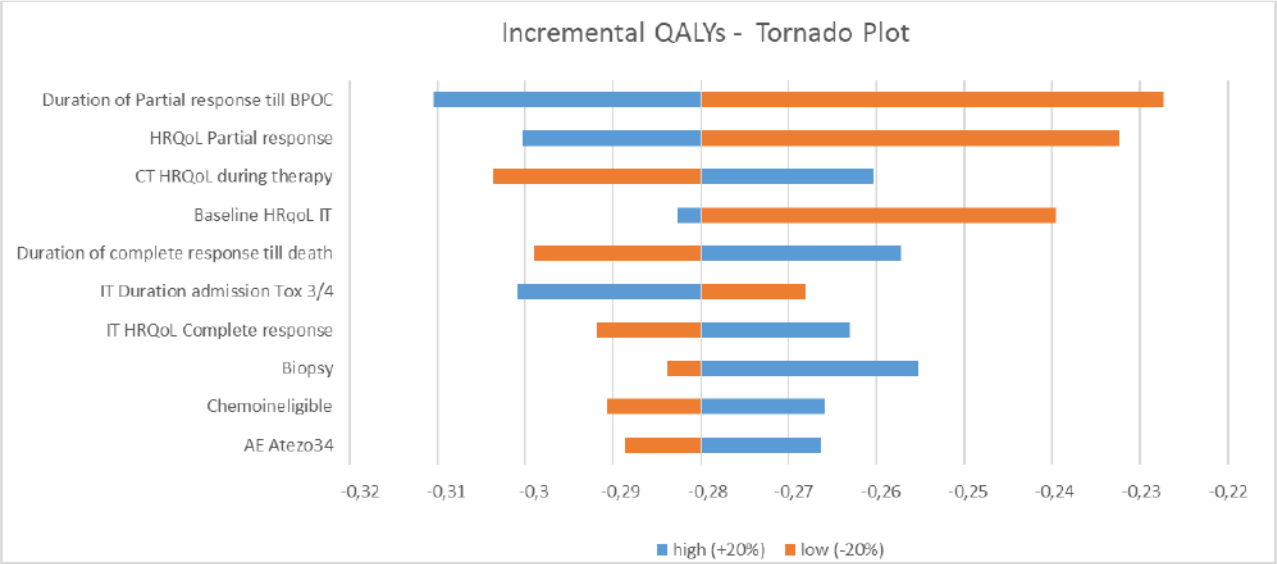

Figure 21: summary tornado plot QALYs

The input parameter duration of partial response till BPOC will affect the outcome the most. This can be declared by the fact that patients who should have responded to immunotherapy, will not receive immunotherapy because of their biomarker values. The incremental QALYs are therefore lower. The same counts for the HRQoL during partial response and the baseline HRQoL for immunotherapy.

Patients who are ineligible for a biopsy or chemotherapy, will receive immunotherapy in the alternative path. When the probability for those patients increase, more responsive patients will receive immunotherapy, and therefore the incremental QALYs increase.

When more adverse events take place while receiving immunotherapy, the current pathway has the most loss in QALY's, since all patients receive immunotherapy in the current pathway.

When more patients are ineligible for a biopsy, the QALY's increase, since those patients receive immunotherapy immediately. And the more patients receive immunotherapy, the more QALYs will increase.

An increase of the HRQoL during chemotherapy leads to an increase in QALYs for the alternative pathway. This is inexplicable, since less patients receive chemotherapy in the alternative pathway, and therefore a decrease would be expected. For the duration of

complete response till death, the outcome is inexplicable as well since more patients in the current pathway benefit from a longer complete response.

6 DISCUSSION

In the first part of this chapter we will discuss the limitations of the research and the model, afterwards we discuss the opportunities to improve the model in further research.

6.1 LIMITATIONS OF THE MODEL

The model we created in this thesis contains a number of limitations. In this chapter we will discuss these limitations and the possibilities to improve them in further research.

The first limitations are those that have to do with the lack of data. Assumptions where necessary to fill the gaps. Based on the literature available, assumptions were made upon the following inputs:

The response rates that are used for cisplatin eligible patients who receive first-line atezolizumab, are based on the response rates from Rosenberg et al. (2016), in which patients received atezolizumab as second line treatment, after failure of chemotherapy When provided as first-line treatment, as in the alternative pathway, response rates are expected to be higher, because the patient's condition has not yet deteriorated. The reverse is the case for the response rates of second-line chemotherapy, in which first-line response rates are used for patients who receive second-line chemotherapy treatment, after failure of immunotherapy.

We made use of a clinical decision algorithm to create multiple subgroups, based on a combination of biomarkers, who were targeted to receive immunotherapy in the first-line treatment. No data available on progression free survival or response for each of these combinatory biomarker subgroups, and we therefore made best possible assumptions for each subgroup regarding response. Literature provided us with progression free survival for the responders and stable diseases.

Because at present, outcome data beyond a follow up after 2 years is lacking, we assumed that patients with a stable disease in time will eventually progress. All the patients in the model with stable disease for 24 months, will progress 5 years after the start of the treatment with a HRQoL of 0.65. In reality those 5 years and the HRQoL will be different for each patient. The same applies for the partial responder, except they have a slightly higher HRQoL. For the complete responders is assumed that they have the same life expectancy as other people of their age. Whether this is the case or not, has yet to be determined.

HRQoL: The values for the HRQoL during treatment are based on the paper of Vaugh et al (2017), and were about the HRQoL during treatment with Pembrolizumab, which is an alternative checkpoint inhibitor targeting the PD-1/PD-L1 axis. We assumed that the HRQoL during treatment with Pembrolizumab and atezolizumab is similar. Assumptions were made about HRQoL during partial response and stable disease after immunotherapy as well. Also HRQoL during BPOC was assumed.

Adverse Events: From literature it is known how often adverse events take place and if so what grade these adverse events are. However, it is not known on what moment these events take place in the treatment. In the model, every patient has a probability on getting an adverse event of grade 1/2 or grade 3/4 during the therapy. Introducing a second adverse event was not possible in our model, due to lack of data, and does not reflect reality. The dropout due to toxicity is also not taken into account. In reality a grade 4 adverse event will certainly lead to dropout, however in the data the probabilities for an adverse event grade 3 and 4 are grouped, and therefore we do not know the probability of and adverse event grade 4.

Costs of immunotherapy: The costs for immunotherapy are only known to the Dutch Minister of public health welfare and sports and the pharmacist, because of the so called “sluis procedure”. In this procedure, very expensive medicines are included, that are promising but maybe cost-ineffective. Because off this “sluis procedure” we do not know the exact costs of atezolizumab.

In the model we did not take into account the deterioration of the patient’s condition during treatment while the patient does not respond. The deterioration can be of influence on the second-line treatment response. This will affect both the current arm and the alternative arm.

The biomarkers that are used are putative biomarkers. Phase 3 studies that were published later on, showed that the biomarkers that are used in the model are of a prognostic nature and of a predictive nature. This makes that the clinical decision algorithm in this thesis should be seen as a format for the future, in which data can be added when available.

There is an important ethical aspect of withholding immunotherapy for patients with unfavourable biomarker characteristics, while there is still a proportion of these patients that will respond to immunotherapy. We cannot determine with high specificity that those patients will not respond. In fact, with the parameters used, 28% of the patients withheld immunotherapy would have had response or a stable disease after having immunotherapy.

In the clinical decision algorithm, patients in whom a biopsy is not possible will be target to the immunotherapy arm. However in practice those patients should receive chemotherapy as first-line treatment and immunotherapy thereafter. This extra arm is not added in the model since we use the same response rates for immunotherapy as first- and second-line treatment and chemotherapy as first- and second-line treatment. Adding the additional arm will therefor make no difference in outcome in the model with the current parameters.

In the sensitivity analysis multiple outcomes are inexplicable. In some cases, costs increase or decrease when adjustments are made for HRQoL parameters, and in other cases the QALYs decrease or increase for when adjustments are made for costs parameters. In the model, costs do not influence HRQoL and vice versa. How these adjustments affect the outcome is not clear. In order to exclude the possibility, that the illogical outcomes where

the result of a too small study population, we ran the simulation with 300.000 patients. The results however where similar.

6.2 Further Research

In order to make the model work in practice, we need a response prediction model, instead of a clinical decision algorithm, where patients are grouped in subgroup. When patient level data would come available it is possible to build such a response prediction model.

Secondly, more reliable data on present biomarkers need to become available, and stronger predictive biomarker (combinations) need to come available, to give a more reliable response prediction. If those biomarkers cannot be integrated in a stronger model, we will still have to deal with the problem that immunotherapy will be wrongfully withheld for to many patients.

7 CONCLUSION

After running the discrete event simulation and analysing the resulting data, the following conclusions can be made:

The first and main task of decision algorithm is to filter out the patients who are most likely not to respond. 37% of the patients will not receive immunotherapy based on their biomarker values. 49% of the patients do receive immunotherapy based on their biomarker values and 14% will receive immunotherapy because a biopsy or chemotherapy was not possible. The sensitivity of the clinical decision algorithm is 63% and the specificity is 47%. The low sensitivity causes a decrease in QALYs because of the high number of false negatives, where a low specificity affects the costs, since non-responders do receive immunotherapy.

In the alternative pathway, the average QALY per patient decreases with 0.28, which is the result of the high number of false negatives. However the average total costs decrease with €17.255. The total savings per QALY are €61.625. This is far higher than the willingness to pay of €24.500.

When the response probabilities are higher for the first-line treatment with atezolizumab, compared to the second-line treatment with atezolizumab, the cost effectiveness of the alternative pathway increase. For an increase of response probability with 20%, the QALYs per patient increase with 0,15 and the costs decrease with €8.871 for the alternative pathway.

When better biomarkers become available in the future, the alternative pathway benefits in term of QALYs, but the costs are about equal. A sensitivity of 85% and a specificity of 90% will result in 0,05 extra QALYs and a decrease in costs of €80. This means that a comparable amount of patients receive immunotherapy, but the response rates for these patients are higher.

A higher sensitivity and specificity of the clinical decision model, a higher response rate for immunotherapy in the first line, or a combination of both, can lead to a more cost effective pathway, where the economic burden can be reduced by saving costs, and the health burden can be reduced by preventing overtreatment and higher response rates for immunotherapy in the first-line treatment for selected patients.

Since there is a lot of uncertainty among the input parameters, a sensitivity analysis is performed. The parameter that influences the net monetary benefit the most are the costs for atezolizumab. An increase of 20% for the atezolizumab costs, results in an increase in monetary benefit of €2.817 i.e. the more expensive atezolizumab is, the more the alternative pathway will benefit. Other biomarkers that affect the net monetary benefit are the HRQoL during partial response, the cost of atezolizumab treatment and the duration of partial response.

With the conclusions above we can give an answer to the research question of this thesis:

"What is the expected health economic impact of selecting for responsive patients for immunotherapy in the first line setting in patients with metastatic urothelial carcinoma using a combination of biomarkers, in comparison to standard therapy that consists of treatment of all comers with chemotherapy in the first-line treatment followed by immunotherapy in the second line?"

Selecting patients with mUC for immunotherapy in the first-line treatment will have a negative effect on the health outcome with a QALY loss of 0.28, but will save €17.255 per patient. The incremental savings per QALY are above the willingness to pay line, which indicates a higher cost-effectiveness, however the QALY decrease is high. When the response probability for immunotherapy is at least 20% higher in the first line, compared to the response probability in the second line, the QALYs will increase and costs decrease. A higher cost-effectiveness ratio is also reached when the sensitivity and the specificity of the decision model increase.

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9 APPENDIX

9.1 APPENDIX A. 7TH EDITION OF TNM CLASSIFICATION (CANCER.NET, 2017)

Tumor (T)

Using the TNM system, the "T" plus a letter and/or number (0 to 4) is used to describe the size and location of the tumor. Some stages are also divided into smaller groups that help describe the tumor in even more detail. If there is more than 1 tumor, the lowercase letter "m" (multiple) is added to the "T" stage category. If the “T” stage starts with a lowercase “c,” it means that the tumor was staged clinically. If it starts with a lowercase “p,” it means that the tumor was staged pathologically. If a patient’s tumor is removed, specific tumor stage information is listed below.

TX:	The primary tumor cannot be evaluated.
T0	(T plus zero): There is no evidence of a primary tumor in the bladder.
Ta:	This refers to noninvasive papillary carcinoma. This type of growth often is found on a small section of tissue that easily can be removed with TURBT.
Tis:	This stage is carcinoma in situ (CIS) or a "flat tumor." This means that the cancer is only found on or near the surface of the bladder. The doctor may also call it non-muscle-invasive bladder cancer, superficial bladder cancer, or noninvasive flat carcinoma. This type of bladder cancer often comes back after treatment, usually as another noninvasive cancer in the bladder.
T1:	The tumor has spread to the connective tissue (called the lamina propria) that separates the lining of the bladder from the muscles beneath, but it does not involve the bladder wall muscle.
T2:	The tumor has spread to the muscle of the bladder wall.
T2a:	The tumor has spread to the inner half of the muscle of the bladder wall, which may be called the superficial muscle.
T2b:	The tumor has spread to the deep muscle of the bladder (the outer half of the muscle).
T3:	The tumor has grown into the *perivesical* tissue (the fatty tissue that surrounds the bladder).
T3a:	The tumor has grown into the perivesical tissue, as seen through a microscope.
T3b:	The tumor has grown into the perivesical tissue macroscopically. This means that the tumor(s) is large enough to be seen during imaging tests or to be seen or felt by the doctor.
T4:	The tumor has spread to any of the following: the abdominal wall, the pelvic wall, a man’s prostate or seminal vesicle (the tubes that carry semen), or a woman’s uterus or vagina.
T4a:	The tumor has spread to the prostate, seminal vesicles, uterus, or vagina.
T4b:	The tumor has spread to the pelvic wall or the abdominal wall.

Node (N)

The “N” in the TNM staging system stands for lymph nodes. These tiny, bean-shaped organs help fight infection. Lymph nodes near where the cancer started, within the true pelvis (called hypogastric, obturator, iliac, perivesical, pelvic, sacral, and presacral lymph nodes), are called regional lymph nodes. Lymph nodes in other parts of the body are called distant lymph nodes.

NX:	The regional lymph nodes cannot be evaluated.
N0	(N plus zero): The cancer has not spread to the regional lymph nodes.
N1:	The cancer has spread to a single regional lymph node in the pelvis.
N2:	The cancer has spread to 2 or more regional lymph nodes in the pelvis.
N3:	The cancer has spread to the common iliac lymph nodes, which are located behind the major arteries in the pelvis, above the bladder

.

Metastasis (M)

The "M" in the TNM system indicates whether the cancer has spread to other parts of the body, called distant metastasis.

M0 :	The disease has not metastasized.
M1:	There is distant metastasis.
M1a:	The cancer has spread only to lymph nodes outside of the pelvis.
M1b:	The cancer has spread other parts of the body.

Stage grouping

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1–N3	M0
	Any T	Any N	M1

From Edge SB, Byrd DR, Compton CC, et al (eds): AJCC Cancer Staging Manual, 7th ed. New York, Springer, 2010.

9.2 APPENDIX B: EXTENSIVE BIOMARKER DATA

Response Atezolizumab cisplatin eligible (Rosenberg et al., 2016)

Response by PD-L1 status

	% of population	ORR [95%CI]	CR	PR	SD	PD	Median OS (95%CI)	12 month OS (95%CI)
IC2/3	32	26% [18–36]	30%	0%	19%	51%	11·4 (9·0–NE)	48% (38–58)
IC1/2/3	65	18% [13–24]	6%	12%	16%	52%		
IC1	35	10% [5–18]	2%	8%	17%	59%	6·7 (5·1–8·8)	30% (20–39)
IC0	33	8% [3–15]	2%	6%	24%	50%	6·5 (4·4–8·3)	29% (20–39)
Total	100	15% [11–19]	5%	10%	19%	51%		

PD-L1 Expression per TCGA subtype

	cluster 1	cluster 2	cluster 3	cluster 4
IC0	47%	28%	11%	9%
IC1	38%	38%	21%	41%
IC2	15%	31%	63%	35%
IC3	0%	3%	5%	15%
Total	100%	100%	100%	100%

	IC0	IC1	IC2	IC3
cluster 1	61%	40%	17%	0%
cluster 2	25%	28%	25%	17%
cluster 3	8%	12%	38%	22%
cluster 4	6%	21%	20%	61%
Total	100%	100%	100%	100%

Response by Mutational load

	All clusters		Luminal				Basal			
			Cluster 1		Cluster 2		Cluster 3		Cluster 4	
	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR
min	0	3	0	4	1	7	1	7	1	5
1quartile	5	10	5	11	5	11	5	12	3	7
median	7	13	7	13	9	13	8	14	5	14
2quartile	11	19	11	20	14	18	11	22	10	20
max	21	24	17	22	21	19	19	22	18	24

Response by TCGA subtype

	cluster 1	cluster 2	cluster 3	cluster 4
PD	61%	42%	78%	56%
SD	29%	24%	6%	24%
PR	9%	20%	11%	14%
CR	1%	14%	5%	6%
Total	100%	100%	100%	100%

Response Atezolizamab cisplatin ineligible	Response by PD-L1 status		% of population	ORR [95%CI]	CR	PR	SD	PD	Median OS (95%CI)	12 month OS (95%CI)		(Balar et al., 2017)
		IC2/3	27	28 [14-47]	12,5	15,6	6	66	12,3(6,0-n.e.)	52%(35-70)		
		IC1/2/3	67	23 [16-31]	10	13,8	10	67				
		IC1	40	24 [15-35]	8,3	12,5	7	69	19,1(9,8-n.e.)	59%(48-70)		
		IC0	32	21 [10-35]	7,6	12,8	5	74	19,1(9,8-n.e.)	59%(48-70)		
		Total	100	21 [9-36]	9,2	13,4			15,9(10,4-n.e.)	57%(48-66)		
	PD-L1 Expression per TCGA subtype		cluster 1	cluster 2	cluster 3	cluster 4			IC0	IC1	IC2	IC3
		IC0	47%	28%	11%	9%		cluster 1	61%	40%	17%	0%
		IC1	38%	38%	21%	41%		cluster 2	25%	28%	25%	17%
		IC2	15%	31%	63%	35%		cluster 3	8%	12%	38%	22%
		IC3	0%	3%	5%	15%		cluster 4	6%	21%	20%	61%
		Total	100%	100%	100%	100%		Total	100%	100%	100%	100%
	Response by Mutational load		Cr	PR	SD	PD						
		min	4	1	1	1						
		1quartile	7	8	2	6						
		median	9	18	7	8						
		2quartile	28	34	11	14						
		max	33	58	21	22						
	Response by TCGA subtype		cluster 1	cluster 2	cluster 3	cluster 4						
		PD	56%	41%	53%	40%						
		SD	17%	25%	26%	40%						
		PR	17%	22%	11%	20%						
		CR	10%	12%	10%	0%						
		Total	100%	100%	100%	100%						

9.3 APPENDIX C: ASSOCIATION OF RESPONSE AND PD-L1 STATUS WITH TCGA AND ML

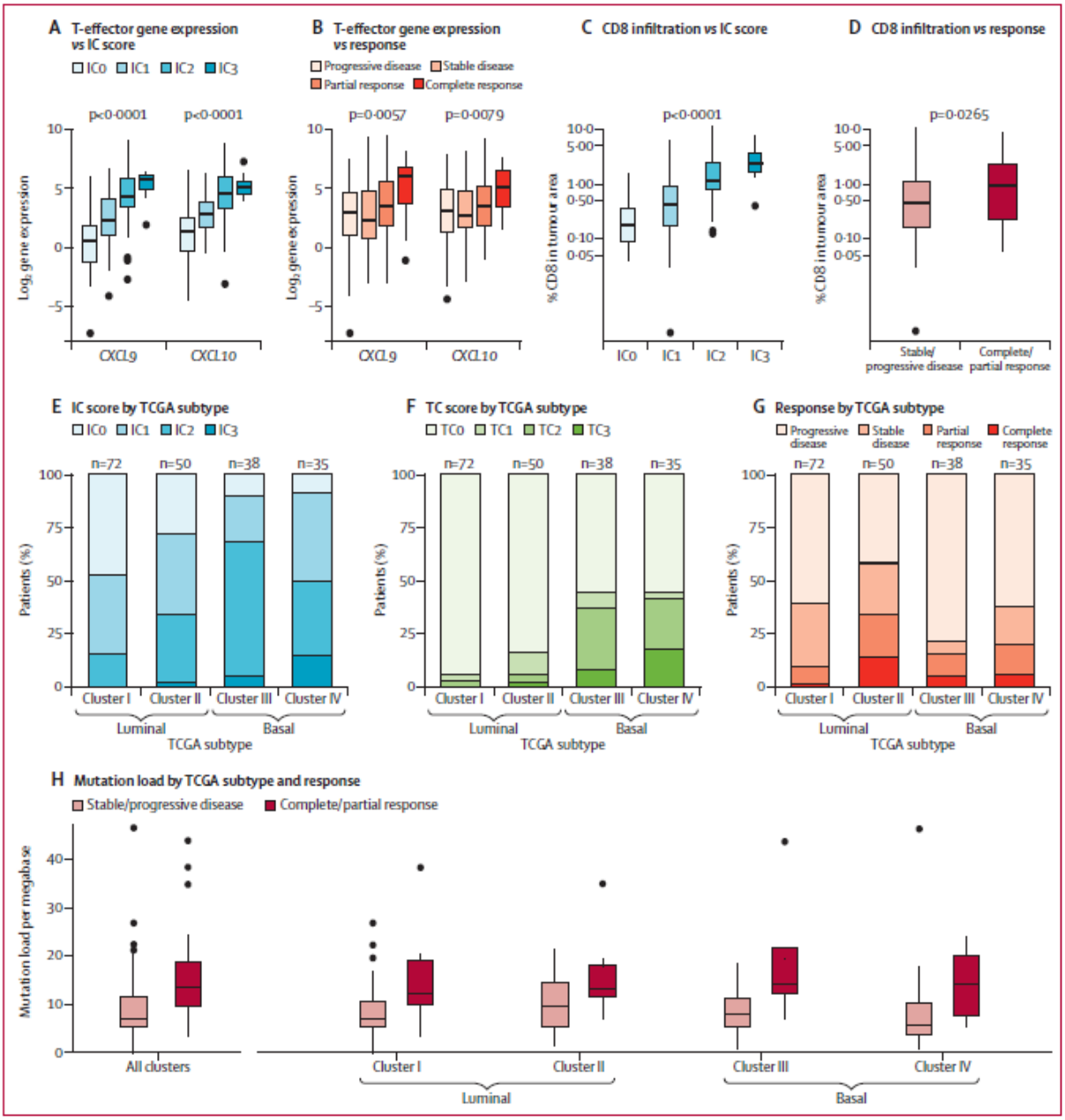


Figure 3: **Association of response and PD-L1 immunohistochemistry status with gene-expression profiling and mutation load**
(A) Association of immune cell PD-L1 immunohistochemistry score with gene expression for *CXCL9* and *CXCL10*, two representatives of a CD8 T-effector gene set. (B) Association of *CXCL9* and *CXCL10* with response to treatment. (C) Association of tumour CD8+ T-cell infiltration in the tumour area and PD-L1 immune cell score. (D) Association of CD8+ immunohistochemistry staining in the tumour area and response to treatment. (E) Immune cell PD-L1 immunohistochemistry score distributions by TCGA subtype. (F) Tumour cell PD-L1 immunohistochemistry score distributions by TCGA subtype. (G) Response distributions by TCGA subtype. (H) Estimated mutation load per megabase versus patient response, overall (n=150) and also disaggregated by TCGA subtype. IC=immune cell. TC=tumour cell. TCGA=The Cancer Genome Atlas.

Figure 22: Response and Biomarkers (Rosenberg et. Al., 2016)

9.4 APPENDIX D: GAMMA DISTRIBUTION FOR MUTATIONAL LOAD

In the table 26, the values for mutational load per TCGA subtype are given.

		CLUSTER 1		CLUSTER 2		CLUSTER 3		CLUSTER 4	
		PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR
MUTATIONAL LOAD BY RESPONSE AND TCGA SUBTYPE	min	0	4	1	7	1	7	1	5
	1quartile	5	11	5	11	5	12	3	7
	median	7	13	9	13	8	14	5	14
	3quartile	11	20	14	18	11	22	10	20
	max	17	22	21	19	19	22	18	24

table 26: ML by TCGA subtype (Rosenberg et al. 2016)

In table 27, the values for Alfa and Beta are calculated using the following formulas.

$$S = \frac{q3 - q1}{1{,}35}$$ (Wan, Wang, Liu, & Tong, 2014)

$$\dot{X} = \frac{q1 + m + q3}{3}$$ (Wan, Wang, Liu, & Tong, 2014)

$$\boldsymbol{\alpha} = \frac{\bar{u}\mathbf{2}}{\boldsymbol{s}\mathbf{2}}$$

$$\boldsymbol{\beta} = \frac{\boldsymbol{s}\mathbf{2}}{\bar{u}}$$

	CLUSTER 1		CLUSTER 2		CLUSTER 3		CLUSTER 4	
	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR	PD/SD	PR/CR
S=(Q3-Q1)/1,35	4,44	6,67	6,67	5,19	4,44	7,41	5,19	9,63
Ẋ=(Q1+M+Q3)/3	7,67	14,67	9,33	14,00	8,00	16,00	6,00	13,67
A = Ū2 / S2	**2,98**	**4,84**	**1,96**	**7,29**	**3,24**	**4,67**	**1,34**	**2,01**
B = S2/ Ū	**2,58**	**3,03**	**4,76**	**1,92**	**2,47**	**3,43**	**4,48**	**6,79**

table 27: parameters Gamma Distribution for ML

9.5 APPENDIX E: ADDITIONAL LIFE EXPECTANCY AFTER COMPLETE RESPONSE:

We want the additional life expectancy for people born in 1952, given they reach the age of 66.

Diagnosis per gender: 20 % female, 80% male (Oncoline, 2009)

The average age at diagnosis is 66 year, which means the patient is born in 1952 (Rosenberg et al., 2016).

We want the additional life expectancy for people born in 1952, given they reach the age of 66. The additional life expectancy for these people is:

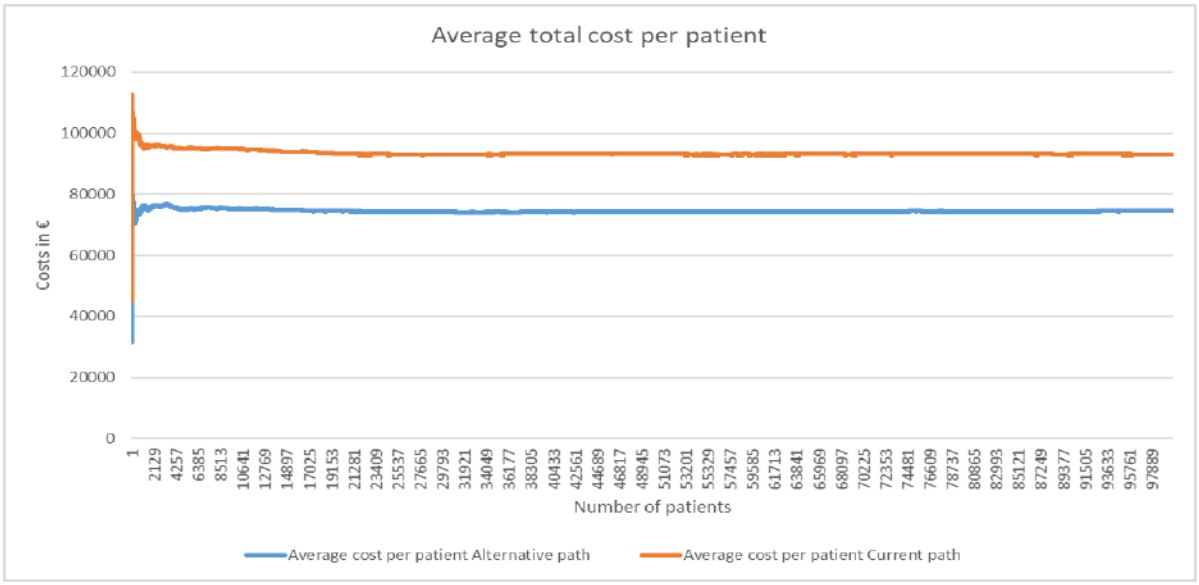
Additional Life expectancy male = 18,3 (CBS, 2018)

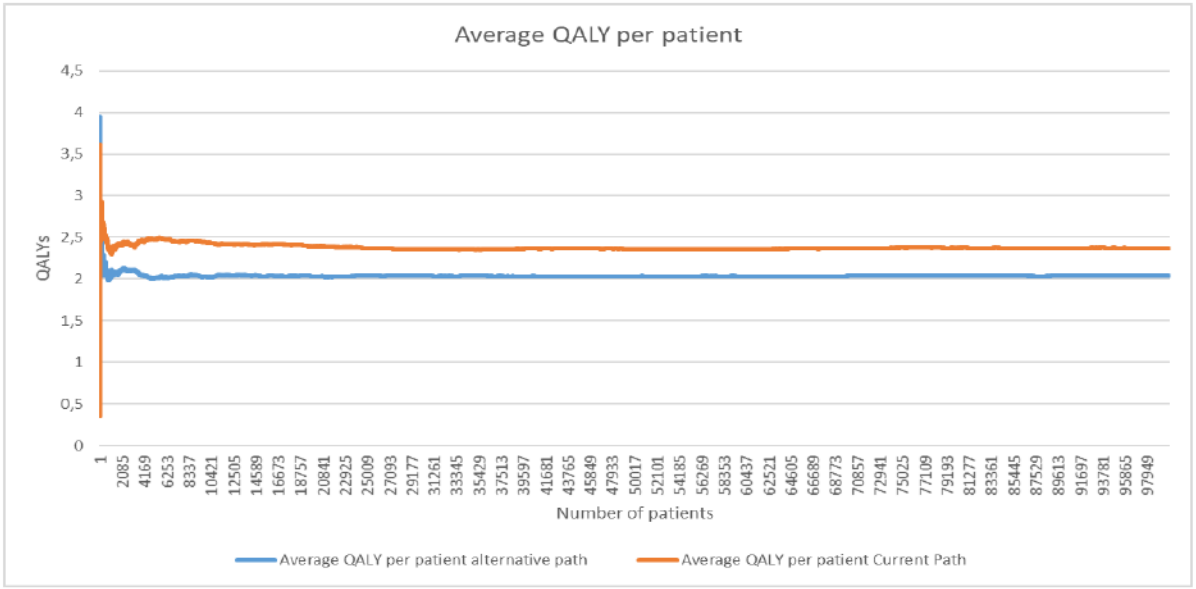
Female = 20,8 (CBS, 2018)

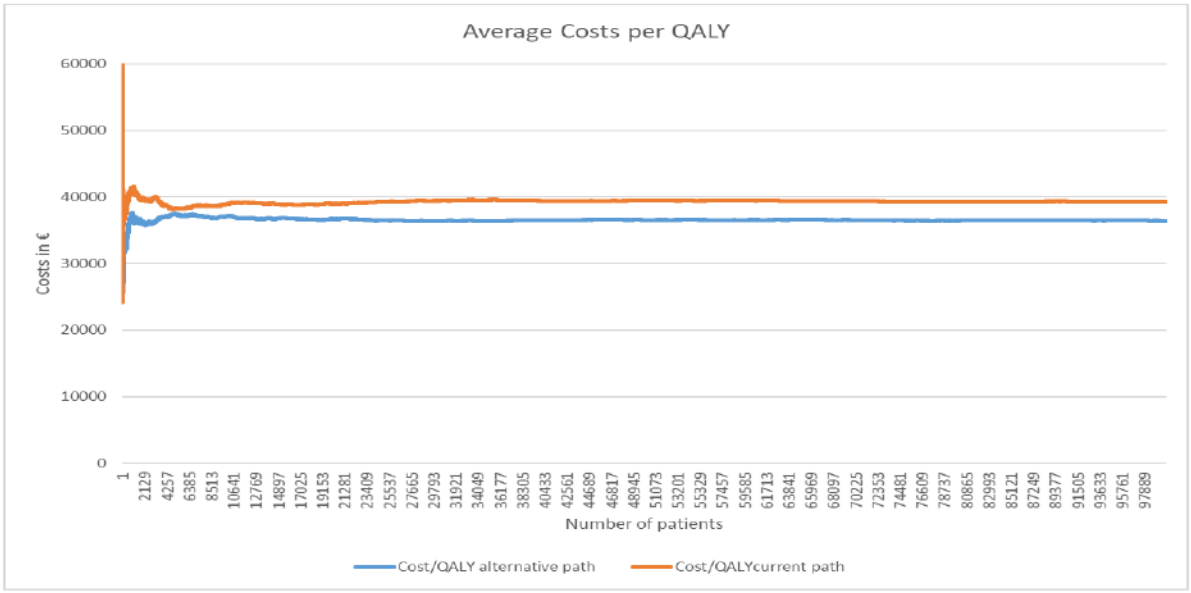
The average number of expanded life years for patients with complete response will be:

$0{,}2 * (20{,}8) + 0{,}8 * (18{,}3) = \mathbf{18{,}8}$ **Years**

9.6 APPENDIX F: NUMBER OF PATIENTS PER RUN







9.7 APPENDIX G: TORNADO DIAGRAMS

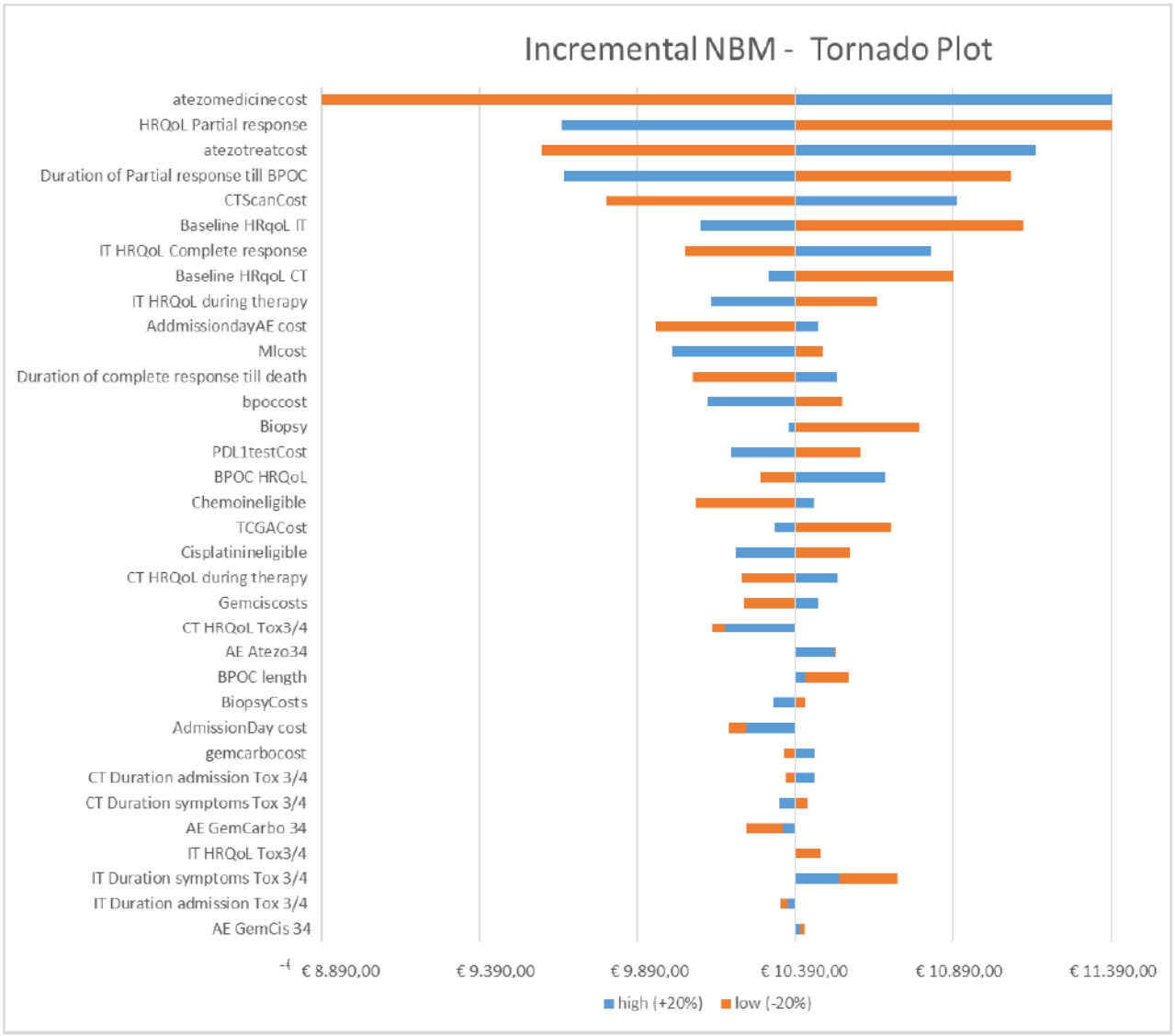


Figure 23: Tornado Plot NBM

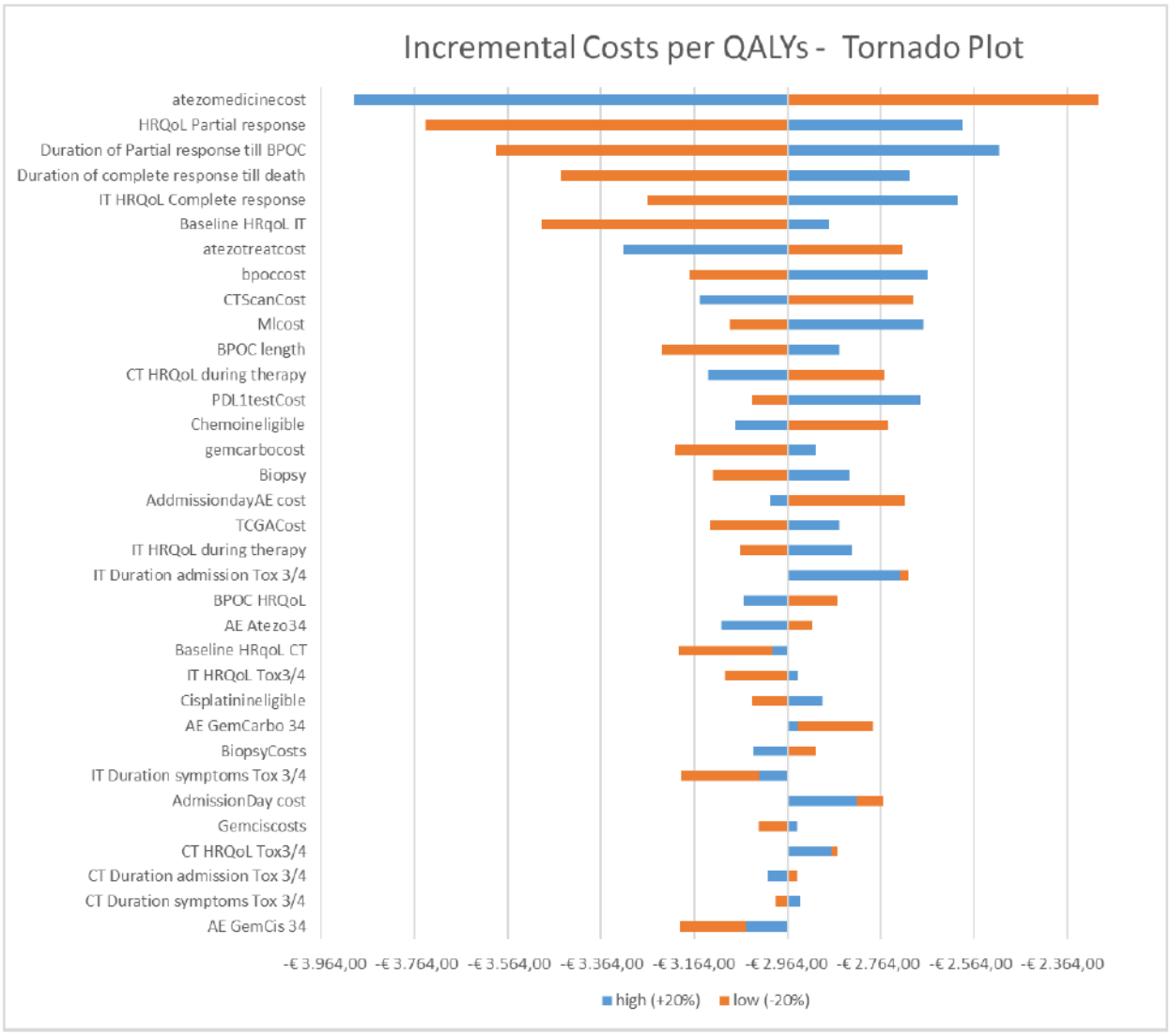


Figure 24: Tornado Plot costs per QALY

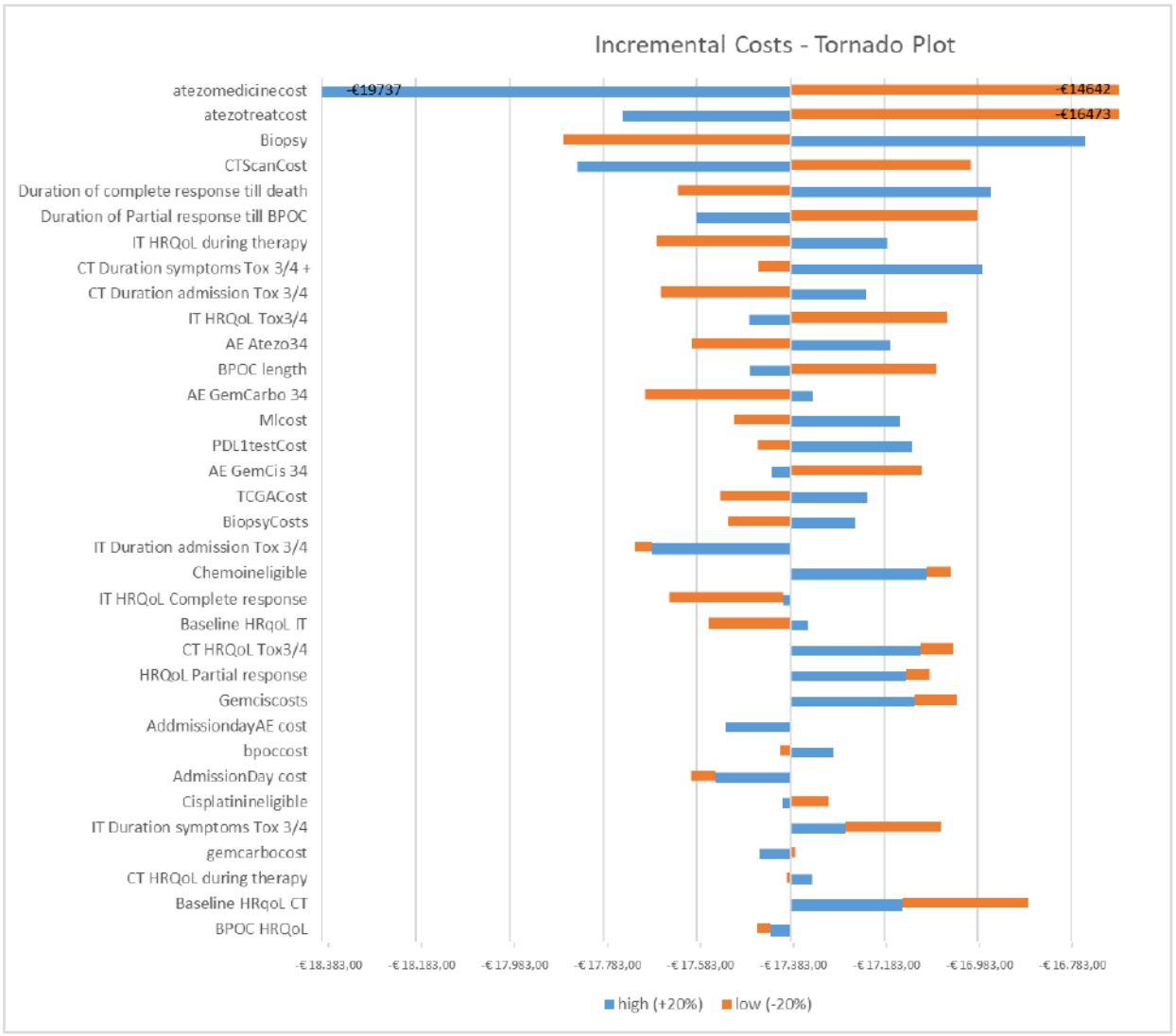


Figure 25: Tornado Plot Costs

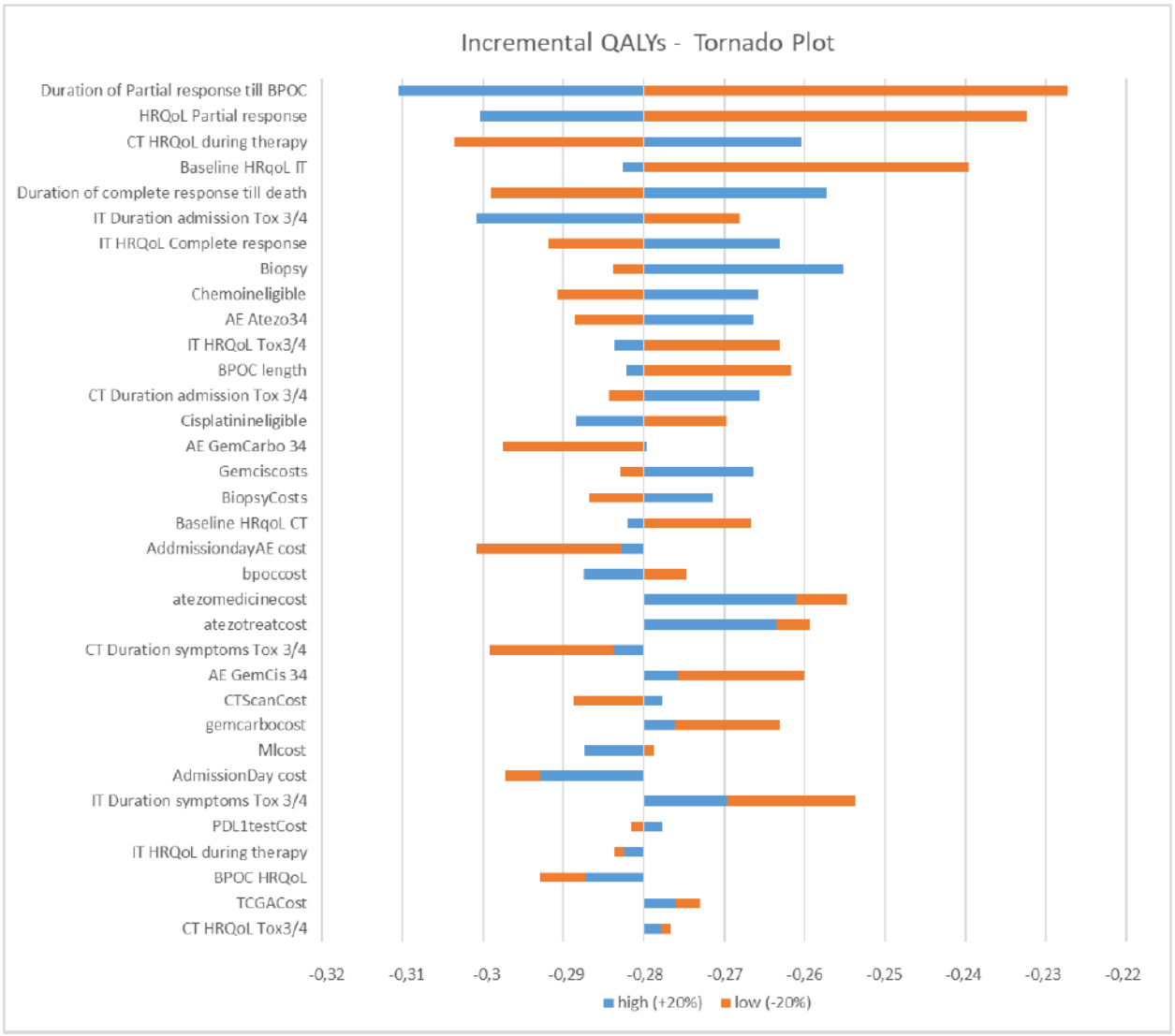


Figure 26: Tornado Plot QALYs