Utrecht Symptom Diary Immunotherapy: patient reported outcomes in patients with melanoma receiving immunotherapy.

Student:	E.G. Verberne
Student number:	4290577
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Supervisor:	Drs. José J. Koldenhof
Docent:	Dr. Thóra B. Hafsteinsdóttir
Contact:	Drs. José J. Koldenhof
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ABSTRACT

Background

Immunotherapy provides new life extending options for patients with advanced melanoma. This treatment can cause serious immune-related toxicities. Early recognition of symptoms is necessary for proactive and adequate symptom management, to prevent aggravation of adverse events and/or admission in hospital. The aim of the study is to provide insight into prevalence of symptoms and symptom intensity, reported by patients by application of the Utrecht Symptom Diary (USD) immunotherapy.

Method

In this retrospective observational study, patient characteristics, disease- and treatment-related data were obtained from medical files. Symptom prevalence, symptom intensity, wellbeing and influence of adverse events (AEs) on quality of life (QoL) were obtained by using the USD immunotherapy. Data was collected between February 2016 and April 2017. For analyses descriptive statistics were used.

Results

A total of 101 USDs were completed by 48 individual patients. Most patients (60.4%) were male and the median age was 62 years. Most patients (66.7%) had melanoma stage IV M1C. Patients were treated with pembrolizumab (56.3%), nivolumab (31.3%) or a combination of ipilimumab and nivolumab (12.4%). The highest symptom intensity was reported on myalgia, arthralgia, pain, sleeping problems, fatigue, reduced activity and wellbeing. Patients on combination treatment also experienced anorexia and tingling. Dry mouth or taste alteration were added by 14.6%. Twelve patients (30%) experienced relevant influence of AEs on QoL. Two patients (4.2%) discontinued their treatment due to immune related toxicities.

Conclusion

The USD immunotherapy provides insight into symptom intensity in patients with advanced melanoma treated with immunotherapy. Early recognition of symptoms is necessary to maintain QoL and to prevent aggravation of immune related toxicities. This increases the opportunity for an optimal, long lasting treatment with immunotherapy.

Keywords: melanoma, immunotherapy, patient reported outcomes, wellbeing, quality of life.

SAMENVATTING

Aanleiding

Immunotherapie biedt nieuwe levensverlengende behandelopties voor patiënten met een melanoom. Deze behandeling kan ernstige immuungemedieerde bijwerkingen veroorzaken. Vroeg signalering van symptomen is van belang om proactief symptoommanagement mogelijk te maken en daarmee verergering van bijwerkingen en/of ziekenhuisopnames te voorkomen. Het doel van dit onderzoek is om inzicht te krijgen in symptoomprevalentie, symptoomintensiteit en welbevinden, gerapporteerd door patiënten met een melanoom, gebruikmakend van het Utrecht Symptoom Dagboek (USD) immunotherapie.

Methode

In dit retrospectieve, observationele onderzoek werden patiëntkarakteristieken, ziekte- en behandel-gerelateerde gegevens verzameld uit medische dossiers. Symptoomprevalentie, symptoomlast, welbevinden en de invloed van bijwerkingen op kwaliteit van leven (KvL) werd gemeten met het USD Immunotherapie. Dataverzameling vond plaats tussen februari 2016 en april 2017. Data analyse werd verricht middels beschrijvende statistiek.

Resultaten

In totaal werden 101 USDs ingevuld door 48 verschillende patiënten. De meeste patiënten waren man (60.4%) en de mediane leeftijd was 62 jaar. De meeste patiënten (66.7%) had een stadium IV M1c melanoom. Patiënten werden behandeld met pembrolizumab (56.3%), nivolumab (31.3%) of een combinatie van ipilimumab met nivolumab (12.4%). De hoogste symptoomintensiteit werd gemeten voor spierpijn, gewrichtspijn, pijn, slaapproblemen, vermoeidheid en verminderde activiteit. Patiënten met de combinatiebehandeling hadden daarnaast last van verminderde eetlust en tintelingen. Twaalf patiënten (30%) ervaarden een relevante invloed van bijwerkingen op KvL. Er waren twee patiënten (4.2%) die permanent de behandeling stopten vanwege immuun-gerelateerde toxiciteit.

Conclusie

Het USD immunotherapie geeft inzicht in de symptoomlast van patiënten met een melanoom die met immunotherapie worden behandeld. Vroegtijdig herkennen van symptomen is van belang om kwaliteit van leven te behouden en verergering van, immuungemedieerde, toxiciteit te voorkomen. Hierdoor wordt de kans op een optimale, langdurige behandeling met immunotherapie vergroot.

Sleutelwoorden: melanoom, immunotherapie, patiënt gerapporteerde uitkomsten, welbevinden, kwaliteit van leven.

INTRODUCTION & RATIONALE

Worldwide melanoma is one of the fastest rising cancers(1). In the Netherlands in 2016, 108.402 patients were diagnosed with cancer from whom 6.787 patients were diagnosed with melanoma. Of these patients 825 died due to melanoma(2). It is expected that incidence of melanoma will increase the coming years(3). Patients with melanoma had poor prognosis and limited treatment options(4,5). A breakthrough was made in 2013, when immunotherapy provided life extending options by stimulating an immune response against cancer cells, which enhanced or altered the immune system(7,8). Nivolumab, pembrolizumab (anti-PD1 checkpoint inhibitors) and ipilimumab (CTLA-4 checkpoint inhibitor) are available types of immunotherapy.

Pembrolizumab and nivolumab, administered every three respectively two weeks, are both prescribed as monotherapy for a maximum treatment duration of two years. Ipilimumab is administered every three weeks with a maximum of four doses and might also be prescribed in combination with nivolumab. Every three weeks patients receive a combination of both therapies for four times, followed by monotherapy nivolumab every two weeks, for a maximum of two years.

Nivolumab and pembrolizumab are preferred, because of their high response rate and lower toxicity compared to ipilimumab monotherapy(7–9). About 20–40% of melanoma patients experience tumor response on anti-PD1 checkpoint inhibitors(10,11). Ipilimumab provides an overall tumor response of 17–35 %(12,13). In patients with brain metastasis (BM) or an increased lactate dehydrogenase level (LDH) response rates decrease(14,15). BM and an increased LDH are known as poor prognostic factors and can be associated with an decreased quality of life (QoL)(13,14). Immunotherapy is still developing, and is nowadays part of standard treatment for patients with melanoma, renal cell carcinoma and non-small cell lung cancer(6,7,16).

Because of the long-lasting treatment period, patients need tolerance for treatment and additional adverse events (AEs)(16). Immunotherapy can cause serious immune-related AEs. Most common skin-related AEs occur (38-62%), including pruritus, rash, dermatitis and vitiligo. Also colitis(18-42%), pneumonitis (9%), musculoskeletal events (6-20%) and endocrine events (11-30%) can occur(8,9,18). Early recognition and insight into symptom prevalence, symptom intensity and wellbeing is necessary for adequate and proactive symptom management, to prevent aggravation of AEs or clinical admission and to maintain QoL(9,19).

In this study disease-related symptoms and AEs are summarized as symptoms, because they both influence patients QoL(17). QoL not only decreases in case of severe

symptoms, but also when multiple mild symptoms are experienced at the same time. In many studies symptoms are described by the view of the professional according to the common terminology criteria for adverse events (CTCAE)(13,20). However healthcare professionals may underestimate the impact of symptoms(17). Self-reported symptoms by patients are considered as the gold standard and the most reliable to measure patients experienced wellbeing and QoL(17,21,22).

The Edmonton Symptom Assessment Scale (ESAS) is a frequently used patient-reported outcome measurement tool (PROM), for early recognizing and monitoring symptoms(22–24). The Utrecht Symptom Diary (USD) is a Dutch translated and modified version of the ESAS(17). Different modules of the USD were developed, targeting different tumor types and/or systemic treatments. The USD immunotherapy is developed to gain insight into self-reported symptoms and symptom intensity in patients receiving immunotherapy(17).

The USD immunotherapy fits with the aim of palliative care to provide personal tailored care, with the focus on QoL(25). At this point there are no studies available reporting on self-reported symptoms and symptom intensity in patients receiving long-term immunotherapy. The aim of the study is to gain insight into symptom prevalence, symptom intensity, wellbeing and influence of AEs on QoL, reported by patients themselves.

RESEARCH QUESTION AND OBJECTIVES

What is the symptom prevalence, symptom intensity, wellbeing and influence of adverse events on quality of life, experienced by patients with advanced melanoma treated with immunotherapy, measured during the first year of treatment by application of the Utrecht Symptom Diary immunotherapy?

Primary objective:
To gain insight into symptom prevalence, symptom intensity and wellbeing in patients perspective.

Secondary objective:
To gain insight into the influence of experienced adverse events on quality of life in patients.

Other objectives:
1. To gain insight into treatment decisions due to symptom prevalence or intensity.

2. To gain insight into treatment decisions experienced by patients with an increased LDH due to symptom prevalence and symptom intensity.

3. To gain insight into treatment decisions experienced by patients with brain metastasis due to symptom prevalence and symptom intensity.

METHODS

Design

This retrospective observational study has a descriptive design and was performed between September 2016 and July 2017. The focus was to describe the objectives as they naturally occurred, experienced by patients with advanced melanoma in daily practice(26). Data was collected from medical files and by application of the USD immunotherapy, during the first year of treatment. For this report the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement was used(27).

Patients

Consecutive sampling was used. The cohort consists of all patients with advanced melanoma (≥18 years of age), treated with nivolumab, pembrolizumab, or a combination of ipilimumab and nivolumab in the outpatient clinic of the Department of Medical Oncology of the University Medical Center Utrecht (UMC)(26).

Patients needed to complete at least one USD immunotherapy during their first year of treatment, which was implemented in February 2016. Patients started treatment between March 2015 and April 2017, and were able and willing to complete the USD immunotherapy by themselves. Patients were able to speak and read in Dutch. An effect size calculation was not necessary, because of the descriptive design. The sample was relatively homogeneous, so a small sample size could be representative(26).

Methods

The primary objective was to determine patient-reported symptoms. Endpoints for this objective were (i) symptom prevalence (ii) symptom intensity and (iii) wellbeing. The secondary objective was to provide insight into the influence of experienced AEs on QoL. The tertiary objective was to investigate treatment decisions. Endpoints for this objective were (i) treatment decisions due to immune-related AEs and disease-related factors, (ii) treatment decisions in patients with an increased LDH level and (iii) treatment decisions in patients with BM.

Data collection

Data was collected at baseline (T=0), three months (T=1), six months (T=2), nine months (T=3) and twelve months (T=4) during the first year of treatment, because every twelve weeks radiologic tumor response evaluation (CT or PET/CT-scan) were performed(6,13,28,29).

At baseline patient characteristics and disease-related data were obtained. Treatment-related data and USD-related data were obtained at each time point (T=0–T=4). Figure 1 provides an overview of the collected data and the corresponding measurements.

{Figure 1}

Data was collected anonymously in Research Online®, which is an online database for small-scale studies, developed by the Julius Center of the UMC in Utrecht. Research Online® provides insight in when data is gathered, which amendments were made and by whom. Data of one extensive case was obtained by two researchers independently, to pilot if Research Online® was properly designed. During this study triangulation was used(26). Data was revised several times, until no amendments were made. Several questions were discussed with the medical oncologist. Besides that, there were research-group meetings, in the presence of five researchers and six student-researchers, where methodological and substantive topics were discussed to gain different insights.

Patient characteristics and disease-related data

At baseline patient characteristics and disease-related data were obtained from medical files. Comorbidities were classified according to American Society of Anesthesiologists Physical Status (ASA) Classification System(30). The stage of melanoma was classified according to tumor, node, metastases (TNM) classification(31).

Treatment

Immunotherapy is prescribed for a maximum treatment duration of two years. During treatment (T=0-4) tumor response evaluations were performed according to the Response Evaluation Criteria In Solid Tumors1.1 (RECIST1.1)(32). At each tumor evaluation the oncologist reported if there was progressive disease, stable disease, partial response or complete response(29,32). Immune-related toxicities are graded according to the CTCAE version 4.03(20).

Patient-reported symptoms and wellbeing

The USD immunotherapy was implemented in February 2016 and consists of 22 0-10 numeric rating scales (NRS), including anorexia, constipation, diarrhea, blood and/or mucus in stool, abdominal pain, cough, visual changes, rash, itch, headache, myalgia, arthralgia, tingling arms/legs, pain, sleeping problems, nausea, anxiety, fatigue, depressed mood, wellbeing and inactivity (0= no burden; 10= worst possible burden). The USD immunotherapy was based on AEs and generic disease-related complaints with a prevalence of ≥10% or potentially serious AEs(8,17). Patients had the opportunity to add missing items and to assign priority to symptoms which needed treatment first. Preferably patients completed an

USD immunotherapy before each administration. All completed USDs three weeks around the tumor evaluation were included.

Some patients started their treatment before implementation of the USD immunotherapy, and others started their treatment after implementation of the USD immunotherapy. For this reason not all patients completed an USD at each time point.

Influence of AEs on QoL

Influence of AEs on QoL was measured by a single-item, answering the question: "To what extent do adverse events influence your quality of life"? on a 0-7 NRS (0= no influence, 7= complete influence in a negative way)(17). This single-item NRS is a valid and reliable measurement tool for measuring QoL(17,33). Baseline USDs were excluded for this item, because patients did not yet received treatment at baseline.

Treatment decisions

Treatment decisions were gathered in medical files referring treatment interruption or discontinuation. Reasons for treatment decisions were reported. In general, in patients with BM or an increased LDH level response rates decrease and treatment decisions were made more often(14,15). Melanoma tends to metastasize to the brain in 5-20% of patients with melanoma of any stage, and in 40-50% in patients with stage IV melanoma(11,14,34). The LDH level is a poor prognostic factor when LDH increased (more than) twice the upper limit of normal (ULN)(11,13,15,35). Treatment decisions were described in patients with and without BM, and in patients with a normal LDH level, ≥1x increased ULN, and ≥2x increased ULN.

Data analysis

Descriptive statistics were performed for analyzing patient characteristics, symptom prevalence, symptom intensity, wellbeing, influence of AEs on QoL and treatment decisions(17,26). To analyze difference in proportion over time the Agresti-Coull confidence interval (CI) of 95% was used, because of the small sample size and the retrospective design(36,37).

For analyzing patient characteristics a median, frequencies and percentages were provided. Symptom prevalence was provided by using prevalence and percentages. Symptom intensity and wellbeing were categorized in mild (≤3), moderate (4≤6), or severe (≥7) symptoms(22,24,38). These categories were made to minimalize the different variables in were the relatively small sample was divided(26). Distinction was made between patients on anti-PD1 checkpoint inhibitors and patients on combination therapy. The influence of AEs on QoL was categorized in mild (1-2), moderate (3-4) or severe (≥5) influence.

For analyzing treatment decisions and immune-related toxicities, distinction was made by treatment (anti-PD1 checkpoint inhibitors and combination therapy) and in patients with or without BM and patients with a normal or increased LDH level. Frequencies and percentages were provided.

Missings

Available case analysis was applied, because all completed USDs were valuable for this study(26,39). Reasons for not completing the USD immunotherapy were reported in a logbook. All cases with observed data were included, because the intention was to describe the objectives at each time point and not to compare different time points in each patient(39).

Ethical approval

This study was conducted according to the principles of Good Clinical Practice, in agreement with the declaration of Helsinki(40), the Dutch law and in general with the Medical Research Involving Human Subjects Acts (WMO)(41).

The USD immunotherapy is part of standard care in daily practice of de Department of Medical Oncology in the University Medical Center Utrecht. The Medical Ethics Committee (METC) confirmed that WMO-permission was not necessary (METC number: 16-755/C). Patients were informed about the USDs being used for scientific research anonymously.

RESULTS

Between March 2015 and April 2017 a total of 52 patients with advanced melanoma received immunotherapy in the outpatient clinic. In this study 48 patients were included. Four patients were excluded because they did not complete an USD immunotherapy in the first year of treatment, or the USD immunotherapy was not completed three weeks around a tumor evaluation. The median monitored treatment duration was 4 months. Table 1 provides patient characteristics and disease related data at baseline.

A total of 101 USDs immunotherapy were completed. Reasons for not completing an USD were serious illness, unwilling to complete an USD because patients stated not to experience serious complaints or no USD was offered. In 17 tumor evaluations the USD immunotherapy was not implemented yet, because patients started their treatment before March 2015.

{Table 1}

Most patients were male (60.4%) and the median age was 62 years. Most patients had comorbidities classified with an ASA II (37.5%), which means that patients had mild systematic disease, were current smoker, social alcohol drinker or obese (30< BMI <40). Seventeen patients (35.4%) had no comorbidities.

There were 23 patients (47.9%) who did not received earlier systematic treatments, like BRAF inhibition (with or without MEK inhibition), immunotherapy, chemotherapy (DTIC) and/or whole brain therapy (WBRT). Fourteen patients (29.2%) received another form of immunotherapy earlier. Most patients had melanoma stage IV M1C (66.7%). In 64.6% melanoma was in relapse. At baseline 34 patients (70.8%) had a normal LDH level. Ten (20.8%) patients had a LDH level ≥1x ULN and four patients (8.3%) had a LDH level ≥2x ULN. There were 13 (27.1%) patients with one or more BMs. Patients were receiving pembrolizumab (56.3%), nivolumab (31.3%) or a combination of ipilimumab and nivolumab (12.4%).

Patient experienced symptoms: prevalence, symptom intensity and wellbeing

Symptoms were reported with a mild, moderate or severe intensity. Symptoms were mainly of mild intensity. Blood/mucus in stool, cough, headache, myalgia, arthralgia and tingling were most frequently reported by patients on anti-PD1 checkpoint inhibitors (figure 2). Symptoms with a moderate or severe score were myalgia, arthralgia, pain, sleeping problems, fatigue, inactivity and wellbeing (figure 3). In patients receiving combination therapy, anorexia and tingling were most frequently reported (figure 4). Symptoms with a

moderate or severe score included sleeping problems, fatigue, depression, inactivity and wellbeing (figure 5).

{Figure 2,3,4 & 5}

Patients were allowed to add missing items in the USD immunotherapy. Dry mouth and taste alteration were added by seven patients (14.6%). These symptoms were also reported in the medical files by physicians and nurses.

Wellbeing is scored in 98 completed USDs; 87 times by 42 patients on anti-PD1 checkpoint inhibitors, and eleven times by six patients on combination therapy. In patients receiving anti-PD1 checkpoint inhibitors, 72 times (82.8%) a mild influenced wellbeing was reported. In 15 USDs (17.2%) patients reported a moderate of severe influenced wellbeing. Patients on combination therapy reported a mild influenced wellbeing for four times (36.4%) and a moderate or severe intensity in seven (63.6%) USDs. In total a moderate or severe influenced wellbeing was reported in 22 (22.4%) completed USDs by 15 individual patients (31.3%).

Influence of AEs on QoL

The single item regarding influence of AEs on QoL was scored 65 times by 40 patients, including 36 patients on anti-PD1 checkpoint inhibitors and four patients on combination therapy. In 29 USDs no influence of AEs on QoL was reported by 21 (52.5%) patients. In sixteen (40.0%) patients AEs had mild influence on QoL and twelve (30.0%) patients reported a moderate or severe influence of AEs on QoL. Table 2 provided insight into scores per patient and in total completed USD forms.

{Table 2}

Figure 6 provided an overview in scores per treatment. Most patients experienced no or mild influence of AEs on QoL. Figure 7 provided insight into scores per time point. At 3 months this item was scored most frequently. Most patients (55%) experienced a mild influenced QoL at three months. There was no significant difference in proportion over time (data not shown) and not as many patients scored the item in each time point.

{Figure 6 & 7}

Treatment decisions

Treatment decisions were referring to treatment interruption or discontinuation, and were made due to patient-experienced and/or healthcare professional-reported symptoms, toxicities or disease-related factors. Eleven times (22.9%) patients interrupted their treatment due to immune-related toxicities, such as headache, arthralgia, myalgia, uveitis or hepatitis.

These patient continued treatment after recovery from the toxicity. Treatment was discontinued in 18 (37.5%) patients, due to progressive disease (31.3%) or toxicity (4.2%). Six patients died during their treatment due to progressive disease. Table 3 provides an overview of treatment decisions and immune-related toxicities.

{Table 3}

Thirteen (27.1%) patients had one or more BMs, from whom three (23.1%) patients interrupted, and seven (53.8%) patients discontinued treatment. There were ten (20.1%) patients with a LDH level ≥1xULN, from who two (20%) patients interrupted, and three (30%) patients discontinued treatment. In patients with a LDH level ≥2x ULN (N=4), no patients interrupted, and two (50%) patients discontinued treatment. There was no significant differences in proportions between patients with/without BM and patients with a normal LDH level or an increased LDH level (data not shown).

DISCUSSION

This retrospective observational study was conducted to gain insight into symptom prevalence, symptom intensity, wellbeing and influence of AEs on QoL, by application of the USD immunotherapy, in patients with advanced melanoma treated with immunotherapy. Mainly patients experienced symptoms of mild intensity, which made treatment sustainable for patients. Symptoms with a moderate or severe intensity were myalgia, arthralgia, pain, sleeping problems, fatigue and inactivity. Fifteen patients (31.3%) experienced relevant influenced wellbeing and 30% experienced a moderate or severe influenced QoL due to AEs. These items correspondents to each other. Only 4.2% permanent discontinued treatment because of immune-related toxicities. As described by Michot et al. most symptoms occurred between the third and the sixth month during treatment(42).

Patients had the opportunity to add symptoms to the USD immunotherapy. Patients added oral problems, including a dry mouth and taste alteration to the USDs, which were also describes in medical files. At the time the USD immunotherapy was developed and implemented, there was nog literature available about oral toxicities in patients receiving immunotherapy. Nowadays, oral toxicities induced by immunotherapy are briefly described in literature. However, it is common in clinical practice(43). Recent studies showed that about 5-20% of patients on immunotherapy experienced oral toxicities, which can lead to a significant morbidity or permanent treatment discontinuation(42,43). In this study 14.6% experienced a dry mouth or taste alteration. Perhaps more patients experienced oral problems, but did not add them to the USDs. Oral toxicities without adequate symptom management may influence QoL, because of social withdrawal and weight loss(44,45). A dry mouth or taste alteration is often accompanied by tough saliva, pain, chewing- and swallowing problems, infections, caries, dental erosion or problems with the dentures. As a result, there is a risk of malnutrition and it may lead to bad breath and speech- or sleeping problems(45,46). There were several patients in this study with loss of appetite and weight loss.

Oral toxicities may be underreported by using general PROMs(43). The USD immunotherapy was based on all AEs and generic disease-related complaints with a prevalence of ≥10% or potentially serious AEs, which means that oral toxicities like a dry mouth and taste alteration can be added in the USD immunotherapy(8,17,43).

Earlier studies gave insight into symptom prevalence by the view of the professional, according to the CTCAE classification(9,13,20). However, literature showed that healthcare professionals may underestimate the impact of symptoms and PROMs are considered as the gold standard(9,17,21,22,47). There is growing interest in integrating PROMs into routine

care, because patient reported symptoms are associated with an increased survival rate(47). Routine symptom assessment is an essential component of qualitative cancer care. PROMs requires a system that provides accurate symptom assessment, that is brief and feasible in clinical practice(48). The USD immunotherapy is such a PROM. At this time healthcare organizations are encouraged to implement PROMs into the electronic medical files(49). During the study, the USD Immunotherapy is implemented into the medical file and patient portal. Patients have access to their own portal at home, so they are able to complete the USD immunotherapy before each administration.

Since 2013, the Dutch Melanoma Treatment Registry (DMTR) is available to assure safety and quality of care in the Netherlands. The DMTR not only collects clinical data, but also data based on patients QoL, by using the EQ-5D, FACT-G and/or FACT-M questionnaires(50,51). These measurement tools are quite extensive and are not feasible to use in daily practice. PROMs needs to be brief and easy to use(48,52). The USD immunotherapy can be completed in about five minutes and might contribute to qualitative and save healthcare and improved symptom management. The USD immunotherapy may contribute the DMTR by providing data from daily practice.

To our knowledge this is the first study reporting on patient experienced symptoms in this vulnerable group of patients. Because the USD immunotherapy is part of standard care in daily practice of de Department of Medical Oncology in the UMC Utrecht, insight is provided into patient experienced symptoms in daily practice. By studying care as usual and using a longitudinal design with consecutive sampling, external validity is maintained(26) Only a few patients permanent discontinued treatment due to toxicities, probably because of early recognition and proactive symptom management in daily care by application of the USD immunotherapy. Since implementation of the USD immunotherapy the focus on patient experienced symptoms increased, so symptoms are proactively managed and patients may better sustain treatment.

This study also has its limitations. Due to the retrospective design data might be missing. Some patients were not able or willing to complete USD forms or there was no USD offered. For this reasons available case analysis was used(26). In general, the medical files were very consequently maintained, which improves the reliability of the study. The descriptive design was chosen because of the small sample size. For this reason it was not possible to compare groups of patients with each other. No significant difference in proportion over time was found, probably because of the small sample size. Another limitation is that data was gathered during the first year of treatment instead of during the first year after implementation of the USD immunotherapy. For this reason not all included

patients completed an USD immunotherapy at each time point, so comparison between time points cannot be made.

To summarize, the USD immunotherapy provides insight into symptom prevalence, symptom intensity, wellbeing and influence of AEs on QoL, experienced by patients with melanoma on immunotherapy. This study might help to improve early recognition of AEs and proactive symptom management, in order to limit treatment decisions and to maintain patients QoL, so they can sustain the long-lasting treatment.

Although the USD immunotherapy provides insight into patients experienced symptoms, oral toxicities are not included yet. Because of the potential consequences and the influence of these toxicities on QoL, the recommendation is to add dry mouth and taste alteration to the USD immunotherapy. Furthermore a prospective study with a mixed method design is recommended, so a larger sample size can be included and difference between groups can be statistically tested. Thereby it is interesting to gain insight into patients experienced QoL with a qualitative design. These insights increases the opportunity for an optimal, long lasting treatment with immunotherapy.

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FIGURES AND TABLES

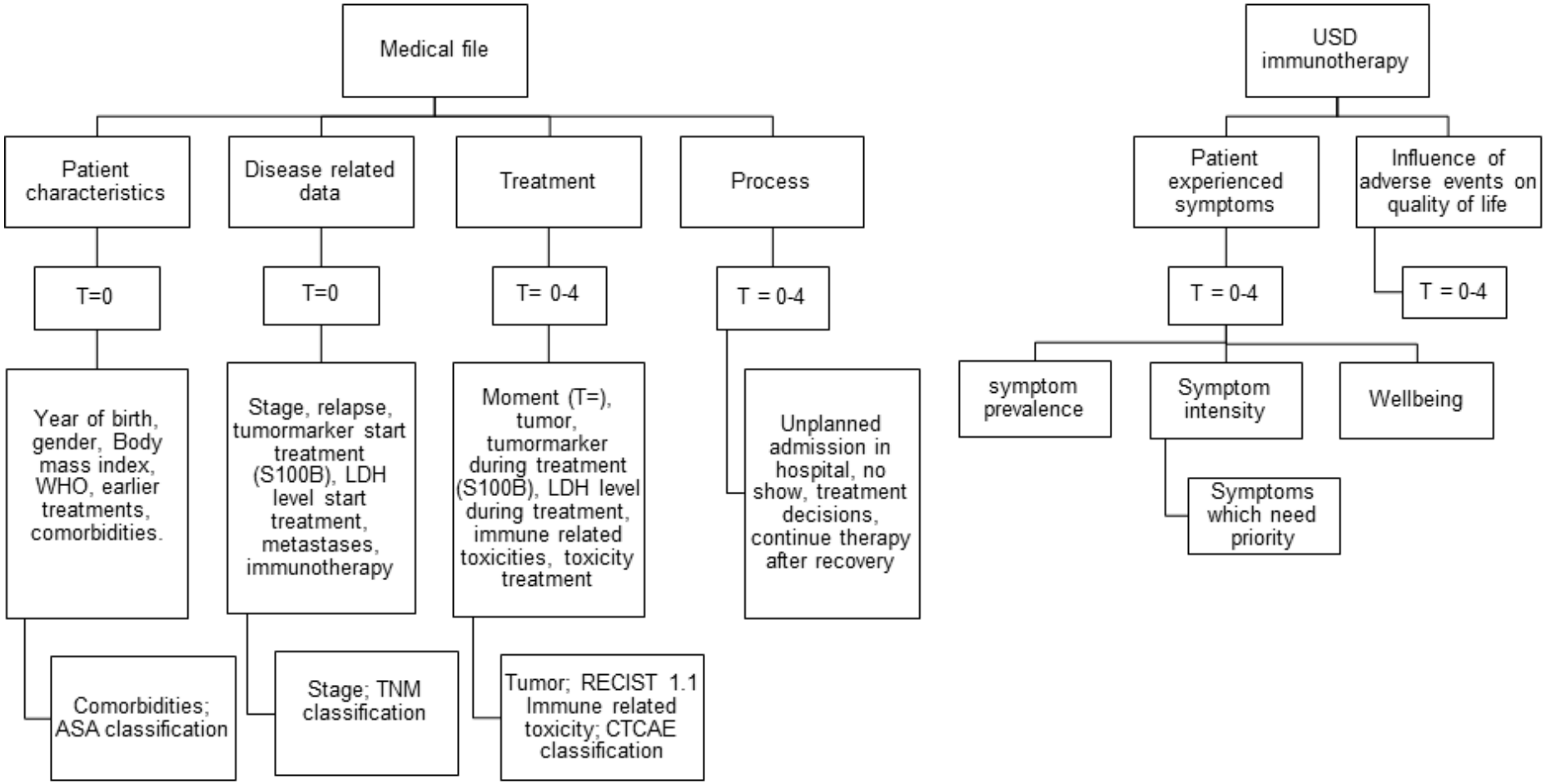

Figure 1: data collection and correspondending measurements.

Table 1: Patient characteristics and disease-related data at baseline (N=48)

Variable	**Prevalence N (%)**
Patients	48
Treatment duration, median (min. – max.)	4 (0.5 – 12)
Completed USD forms	101
Gender	
Male	29 (60.4%)
Female	19 (39.6%)
Age, median (min. – max.)	62 (38 – 86)
Comorbidities	
ASA classification*	
ASA I	17 (35.4%)
ASA II	18 (37.5%)
ASA III	13 (27.1%)
Earlier treatments	
None	23 (47.9%)
BRAF inhibition	8 (16.7%)
Immunotherapy	14 (29.2%)
Other**	4 (8.3%)
Stage of melanoma	
IIIA	0 (0.0%)
IIIB	2 (4.2%)
IIIC	1 (2.1%)
IV M1a	11 (22.9%)
IV M1b	2 (4.2%)
IV M1c	32 (66.7%)
Relapse	
No	17 (35.4%)
Yes	31 (64.6%)
LDH level	
Normal (0-250)	34 (70.8%)
≥1 x increased (251-500)	10 (20.8%)
≥2 x increased (≥501)	4 (8.3%)
Metastasis ***	
None	1 (2.1%)
Pulmonary	19 (39.6%)
Liver	14 (29.2%)
Brain	13 (27.1%)
(sub)Cutaneous	18 (37.5%)
Lymph node	48 (83.3%)
Other	
Bone	12 (25.0%)
Gastrointestinal	12 (25.0%)
Renal	6 (12.5%)
Cardiovascular	6 (12.5%)
Immunotherapy	
Nivolumab	15 (31.3%)
Pembrolizumab	27 (56.3%)
Ipilimumab and nivolumab	6 (12.4%)

* ASA: American Society of Anesthesiologists Physical Status Classification System. ASA I = normal healthy person, ASA II patient with mild systemic disease, ASA III patient with severe systemic disease, ASA IV patient with severe systemic disease that is a constant treat to life, ASA V a moribund patient who is not expected to survive without operation, ASA VI a declared brain-dead patient whose organs are being removed for donor purposes. Scores are based on: BMI ≥30, current smoker, social drinker, cardiovascular disease, diabetes mellitus, COPD, BMI ≥40, renal insufficiency, hypothyroid, hepatitis, pulmonary embolism.
** Dacarbazine (DITC) and MEK inhibition.
*** Most common metastasis.

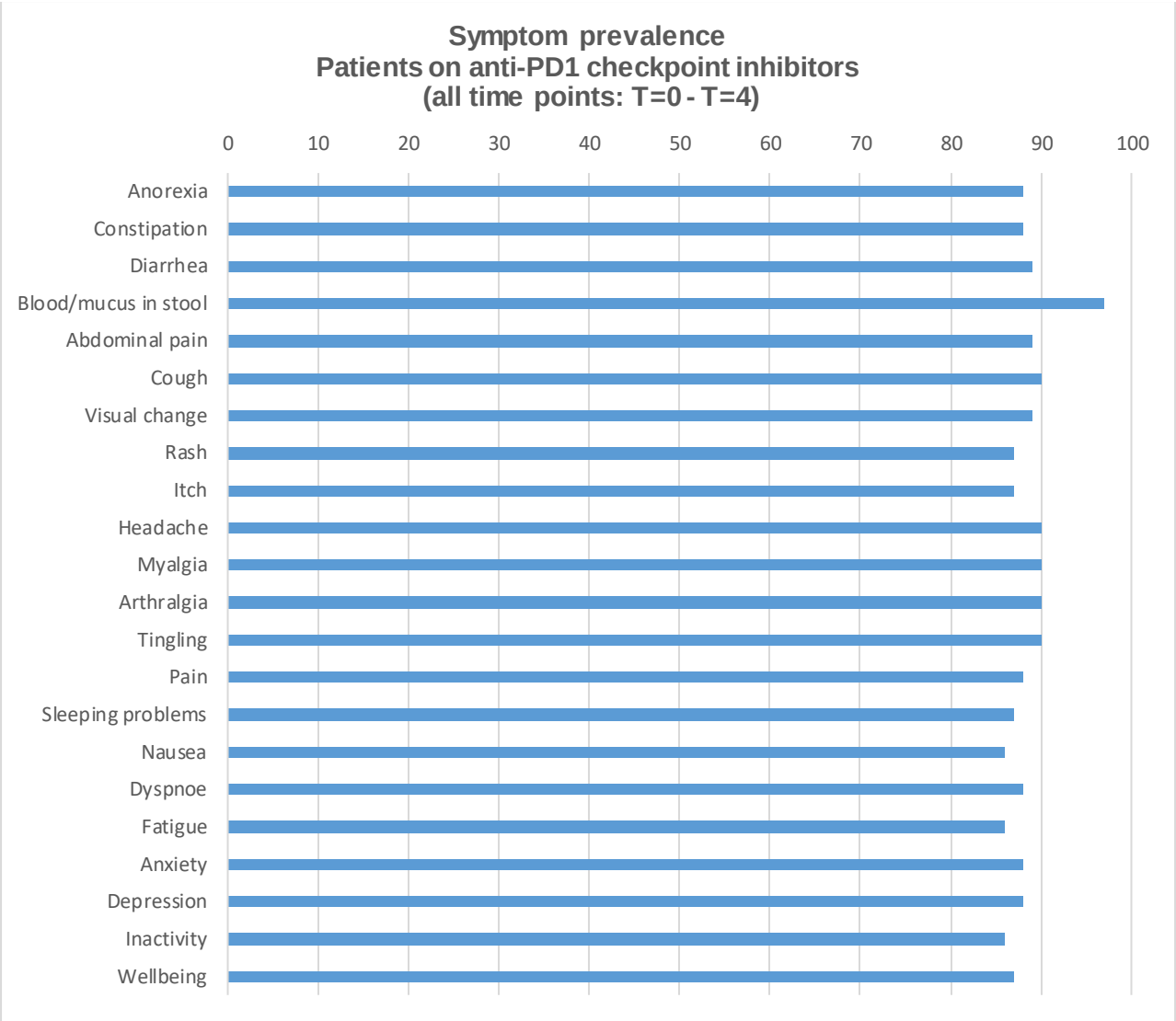

Figure 2: Symptom prevalence in patients on anti-PD1 checkpoint inhibitors.

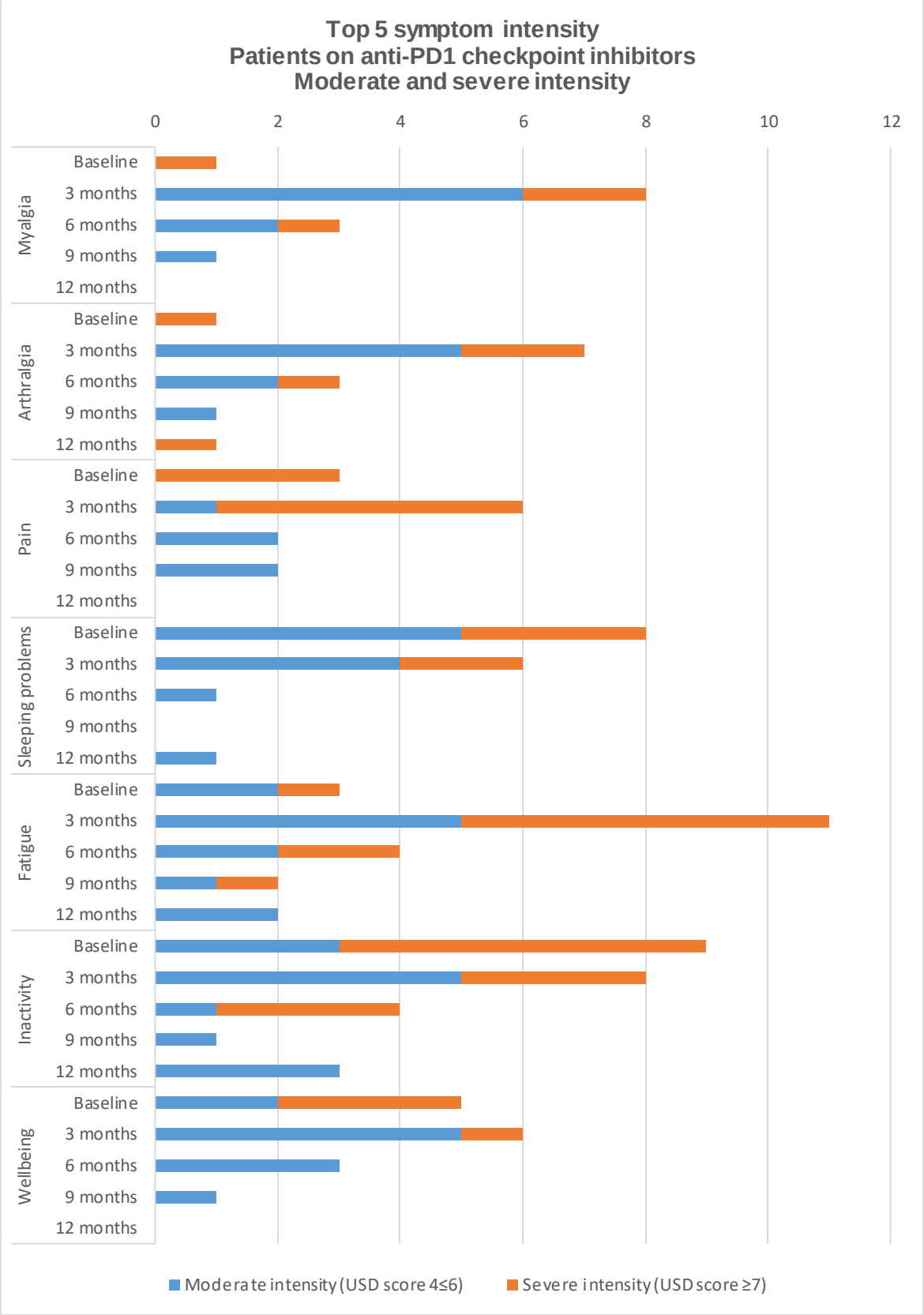

Figure 3: Top 5 symptom intensity in patients on anti-PD1 checkpoint inhibitors; moderate and severe intensity.

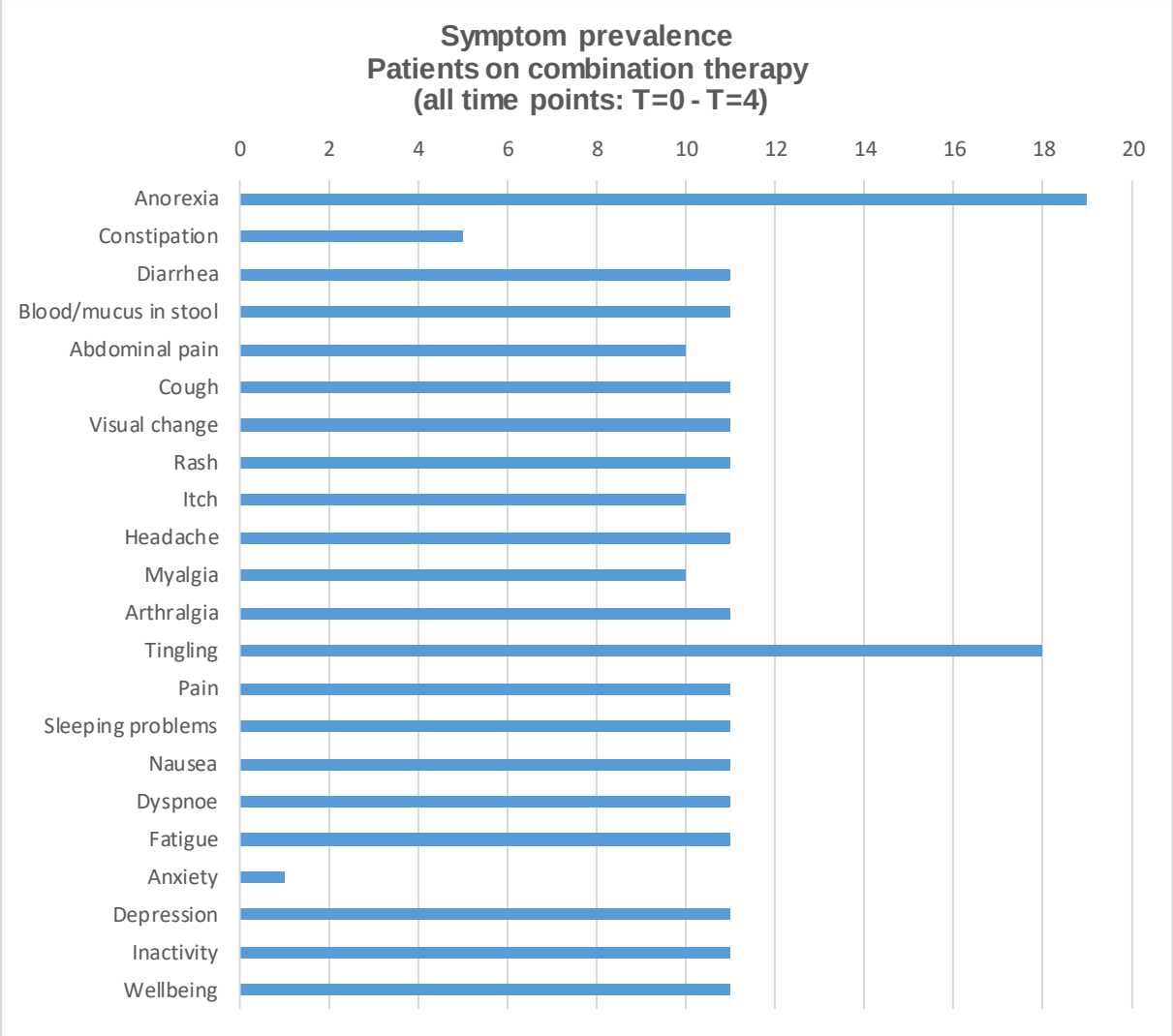

Figure 4: Symptom prevalence in patients on combination therapy.

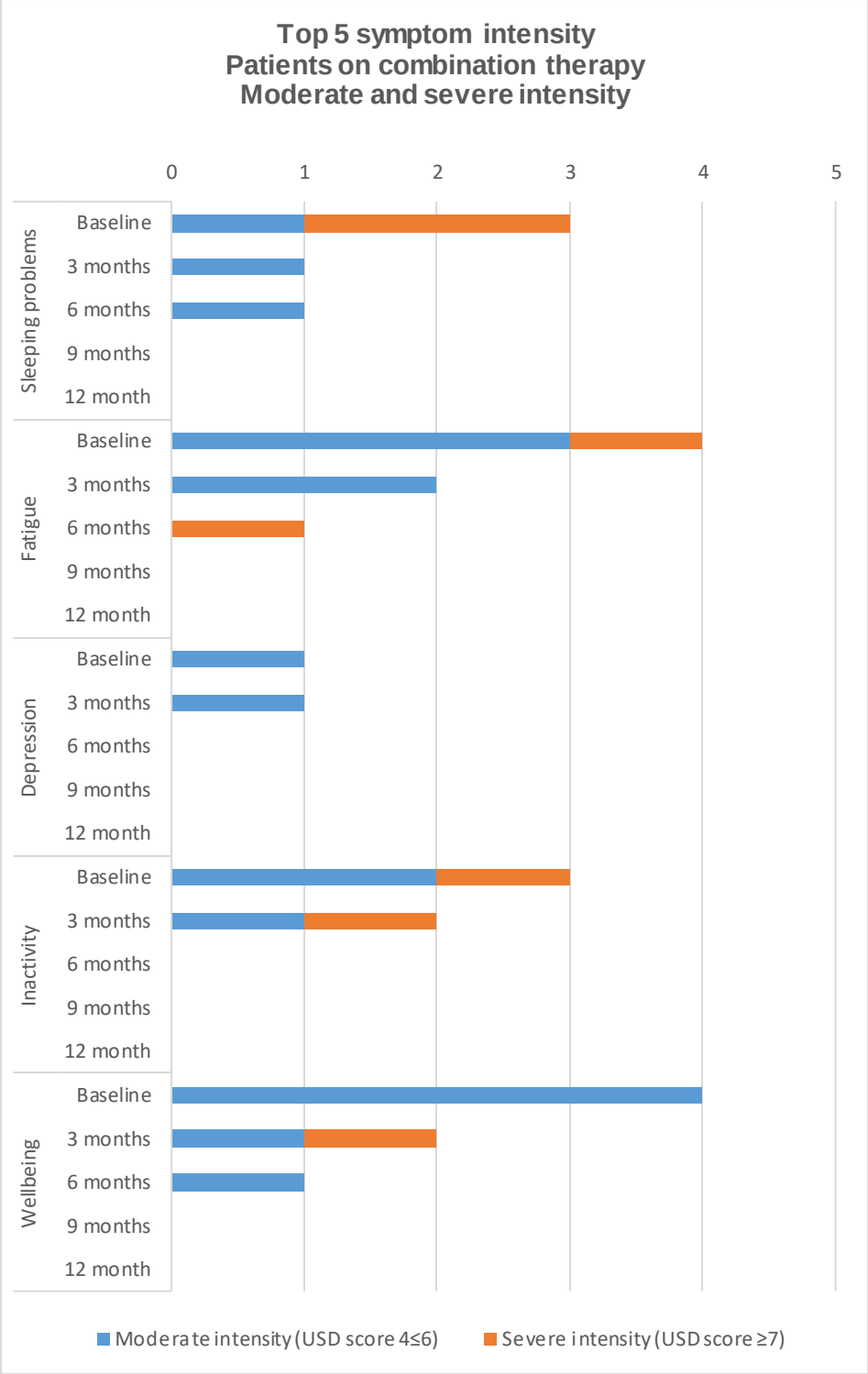

Figure 5: Top 5 symptom intensity in patients on combination therapy; moderate and severe intensity.

The extensive table about symptom prevalence and symptom intenstiy can be found in appendix 1.

Table 2: Influence of AEs on QoL, scored by individual patients N(%), and scores in completed USD forms.

USD Scores	Anti-PD1 checkpoint inhibitors N(%)	Anti-PD1 checkpoint inhibitors (USD forms)	Combination therapy N(%)	Combination therapy (USD forms)	Total N(%)
0	20 (55.5%)	27 (41.5%)	1 (25%)	2 (3.1%)	21 (52.5%)
1-2 (mild)	15 (41.7%)	21 (32.3%)	1 (25%)	1 (1.5%)	16 (40.0%)
3-4 (moderate)	6 (16.7%)	8 (12.3%)	1 (25%)	1 (1.5%)	7 (17.5%)
≥5 (severe)	4 (11.1%)	4 (6.2%)	1 (25%)	1 (1.5%)	5 (12.5%)

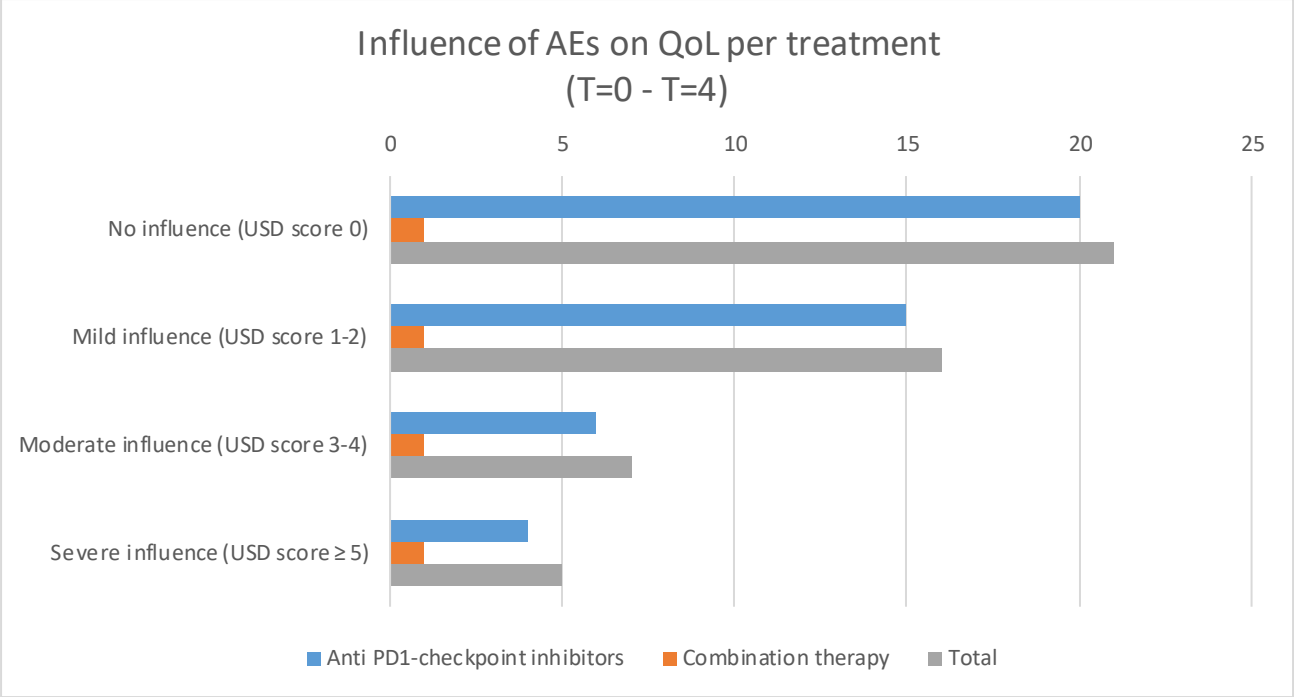

Figure 6: Influence of AEs on QoL per treatment.

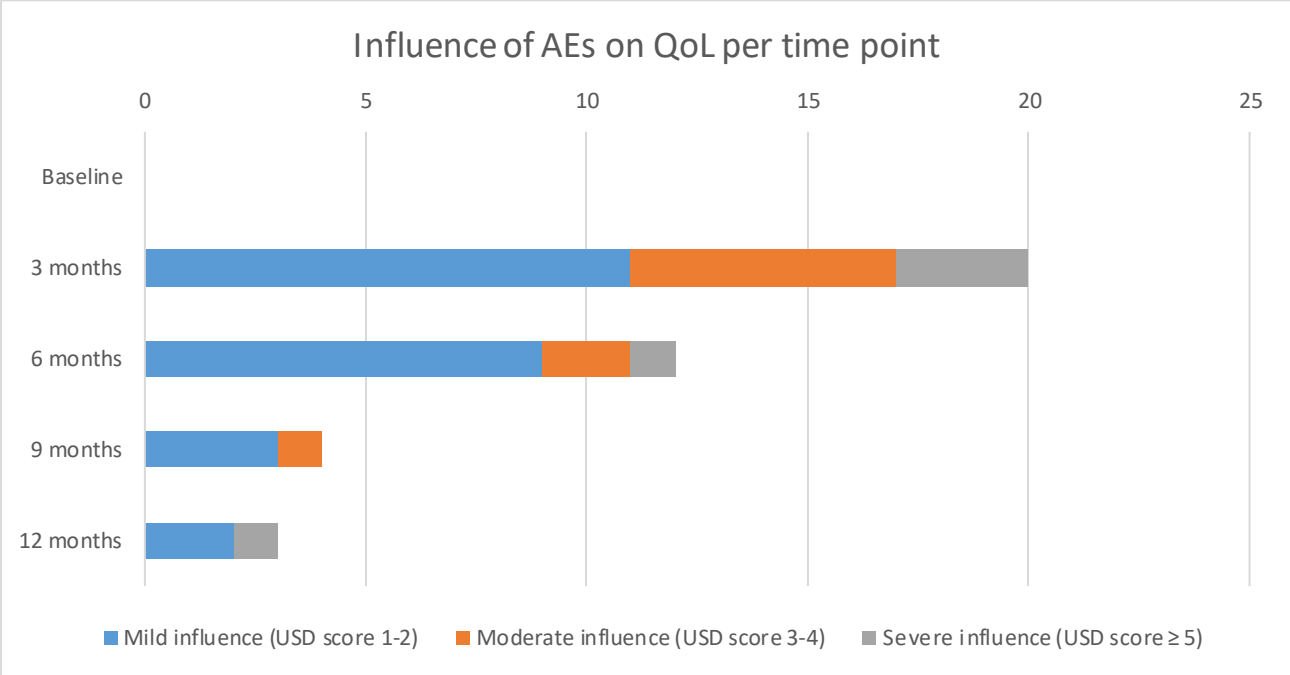

Figure 7: Influence of AEs on QoL per time point.

Table 3: treatment decisions and immune-related toxicities

Anti-PD1 checkpoint inhibitors

	Interruption	Discontinuation
Overall (N= 42)	10 (23.8%)	16 (38.1%)
BM - (N= 32)	9 (28.1%)	10 (31.3%)
BM + (N= 10)	2 (20.0%)	5 (50.0%)
Normal LDH level (N= 33)	10 (30.3%)	12 (36.4%)
LDH level ≥1 x ULN (N= 9)	1 (11.1%)	3 (27.0%)
LDH level ≥2 x ULN (N= 0)	0 (0.0%)	0 (0.0%)
Reasons		
Toxicity	10 (100%)	2 (12.5%)
Headache	2	
Arthralgia	3	
Colitis	1	
Uveitis	2	1
Myalgia	2	1
Hyperthyreoïdie	1	
Hypothyreoïdie	1	
Hepatitis	1	
Pancreatitis	1	
Dermatitis/Rash	1	
Nefritis	1	
Fatigue	1	
Abdominal pain	1	
Visual changes	1	
Progressive disease		13 (81.3%)
Death		4
Completed two years of treatment		1

Combination therapy

	Interruption	Discontinuation
Overall (N=6)	1 (16.7%)	2 (33.3%)
BM - (N=3)	0 (0.0%)	0 (0.0%)
BM + (N=3)	1 (33.3%)	2 (66.7%)
Normal LDH level (N= 1)	0 (0.0%)	0 (0.0%)
LDH level ≥1 x ULN (N= 1)	1 (100%)	0 (0.0%)
LDH level ≥2 x ULN (N=4)	0 (0.0%)	2 (50.0%)
Reasons		
Toxicity	1 (100%)	
Pneumonitis	1	
Hepatitis	1	
Progressive disease		2 (100%)
Death		2

APPENDIX 1: EXTENSIVE TABLES SYMPTOM PREVALENCE AND INTENSITY

Table 4: Symptom prevalence, symptom intensity and wellbeing

	Patients on anti-PD1 checkpoint inhibitors				
Symptom and symptom intensity	**Baseline (T=0) (N=42) N (%)**	**3 months (T=1) (N=42) N (%)**	**6 months (T=2) (N= 27) N (%)**	**9 months (T=3) (N= 14) N (%)**	**12 months (T=4) (N= 10) N (%)**
Anorexia					
USD score 0≤3	19 (45%)	25 (60%)	17 (63%)	9 (69%)	7 (70%)
USD score 4≤6	1 (2%)	3 (7%)	0	0	0
USD score ≥7	4 (10%)	2 (5%)	1 (4%)	0	0
Missings	18 (43%)	12 (29%)	9 (33%)	4 (31%)	3 (30%)
Constipation					
USD score 0≤3	18 (43%)	27 (64%)	16 (59%)	10 (77%)	7 (70%)
USD score 4≤6	3 (7%)	1 (2%)	0	0	0
USD score ≥7	4 (10%)	1 (2%)	1 (4%)	0	0
Missings	17 (40%)	13 (31%)	10 (37%)	3 (23%)	3 (30%)
Diarrhea					
USD score 0≤3	25 (57%)	26 (62%)	17 (63%)	9 (69%)	7 (70%)
USD score 4≤6	0	3 (7%)	0	0	0
USD score ≥7	2 (5%)	0	0	0	0
Missings	17 (39%)	13 (31%)	10 (37%)	4 (31%)	3 (30%)
Blood/mucus stool					
USD score 0≤3	24 (49%)	30 (71%)	18 (67%)	10 (77%)	7 (70%)
USD score 4≤6	0	0	0	0	0
USD score ≥7	8 (16%)	0	0	0	0
Missings	17 (35%)	12 (29%)	9 (33%)	3 (23%)	3 (30%)
Abdominal pain					
USD score 0≤3	24 (57%)	28 (67%)	16 (59%)	10 (77%)	7 (70%)
USD score 4≤6	1 (2%)	1 (2%)	1 (4%)	0	0
USD score ≥7	0	1 (2%)	0	0	0
Missings	17 (40%)	12 (29%)	10 (37%)	3 (23%)	3 (30%)
Cough					
USD score 0≤3	21 (50%)	29 (69%)	17 (63%)	9 (63%)	7 (70%)
USD score 4≤6	2 (5%)	0	1 (4%)	1 (8%)	0
USD score ≥7	2 (5%)	1 (2%)	0	0	0
Missings	17 (40%)	12 (29%)	9 (33%)	3 (23%)	3 (30%)

Visual changes					
USD score 0≤3	23 (55%)	27 (64%)	17 (63%)	10 (77%)	6 (60%)
USD score 4≤6	1 (2%)	1 (2%)	0	0	1 (10%)
USD score ≥7	1 (2%)	2 (5%)	0	0	0
Missings	17 (40%)	12 (29%)	10 (37%)	3 (23%)	3 (30%)
Skin change					
USD score 0≤3	25 (60%)	27 (64%)	16 (59%)	8 (62%)	7 (70%)
USD score 4≤6	0	2 (5%)	1 (4%)	0	0
USD score ≥7	0	1 (2%)	0	0	0
Missings	17 (40%)	12 (29%)	10 (37%)	5 (38%)	3 (30%)
Rash					
USD score 0≤3	24 (57%)	27 (64%)	15 (56%)	8 (62%)	5 (50%)
USD score 4≤6	0	3 (7%)	1 (4%)	0	1 (10%)
USD score ≥7	1 (2%)	0	0	1 (8%)	1 (10%)
Missings	17 (40%)	12 (29%)	11 (41%)	4 (31%)	3 (30%)
Headache					
USD score 0≤3	24 (57%)	29 (69%)	18 (64%)	9 (69%)	6 (60%)
USD score 4≤6	0	1 (2%)	1 (4%)	0	1 (10%)
USD score ≥7	1 (2%)	0	0	0	0
Missings	17 (40%)	12 (29%)	9 (32%)	4 (31%)	3 (30%)
Myalgia					
USD score 0≤3	24 (57%)	22 (52%)	15 (56%)	9 (69%)	7 (70%)
USD score 4≤6	0	6 (14%)	2 (7%)	1 (8%)	0
USD score ≥7	1 (2%)	2 (5%)	1 (4%)	0	0
Missings	17 (40%)	12 (29%)	9 (33%)	3 (23%)	3 (30%)
Arthralgia					
USD score 0≤3	24 (57%)	23 (55%)	15 (56%)	9 (69%)	6 (60%)
USD score 4≤6	0	5 (12%)	2 (7%)	1 (8%)	0
USD score ≥7	1 (2%)	2 (5%)	1 (4%)	0	1 (10%)
Missings	17 (40%)	12 (29%)	9 (33%)	3 (23%)	3 (30%)
Tingling					
USD score 0≤3	23 (55%)	27 (64%)	18 (67%)	9 (69%)	6 (60%)
USD score 4≤6	1 (2%)	2 (5%)	0	1 (8%)	0
USD score ≥7	1 (2%)	1 (2%)	0	0	1 (10%)
Missings	17 (40%)	12 (29%)	9 (33%)	3 (23%)	3 (30%)
Pain	‘				
USD score 0≤3	22 (52%)	24 (57%)	15 (56%)	8 (62%)	6 (60%)
USD score 4≤6	0	1 (2%)	2 (7%)	2 (15%)	0
USD score ≥7	3 (7%)	5 (12%)	0	0	0
Missings	17 (40%)	12 (29%)	10 (37%)	3 (23%)	4 (40%)

Sleeping problems					
USD score 0≤3	17 (40%)	24 (57%)	15 (56%)	9 (69%)	6 (60%)
USD score 4≤6	5 (12%)	4 (10%)	1 (4%)	0	1 (10%)
USD score ≥7	3 (7%)	2 (5%)	0	0	0
Missings	17 (40%)	12 (29%)	11 (41%)	4 (31%)	3 (30%)
Nausea					
USD score 0≤3	23 (55%)	29 (69%)	16 (59%)	9 (69%)	7 (70%)
USD score 4≤6	1 (2%)	0	0	0	0
USD score ≥7	1 (2%)	0	0	0	0
Missings	17 (40%)	13 (31%)	11 (41%)	4 (31%)	3 (30%)
Dyspnea					
USD score 0≤3	24 (57%)	29 (69%)	18 (67%)	9 (69%)	7 (70%)
USD score 4≤6	0	0	0	0	0
USD score ≥7	1 (2%)	. 0	0	0	0
Missings	17 (40%)	13 (31%)	9 (33%)	4 (31%)	3 (30%)
Fatigue					
USD score 0≤3	22 (52%)	17 (40%)	13 (48%)	7 (54%)	5 (50%)
USD score 4≤6	2 (4%)	5 (12%)	2 (7%)	1 (8%)	2 (20%)
USD score ≥7	1 (2%)	6 (14%)	2 (7%)	1 (8%)	0
Missings	10 (40%)	14 (33%)	10 (37%)	4 (31%)	3 (30%)
Anxiety					
USD score 0≤3	22 (52%)	27 (64%)	17 (63%)	8 (62%)	7 (70%)
USD score 4≤6	1 (2%)	2 (5%)	1 (4%)	0	0
USD score ≥7	2 (5%)	0	0	1 (8%)	0
Missings	17 (40%)	13 (31%)	9 (33%)	4 (31%)	3 (30%)
Gloom					
USD score 0≤3	24 (57%)	27 (64%)	18 (67%)	8 (62%)	7 (70%)
USD score 4≤6	0	1 (2%)	0	1 (8%)	0
USD score ≥7	1 (2%)	1 (2%)	0	0	0
Missings	17 (40%)	13 (31%)	9 (33%)	4 (31%)	3 (30%)
Inactivity					
USD score 0≤3	15 (37%)	21 (50%)	13 (48%)	8 (62%)	4 (40%)
USD score 4≤6	3 (7%)	5 (12%)	1 (4%)	1 (8%)	3 (30%)
USD score ≥7	6 (15%)	3 (7%)	3 (11%)	0	0
Missings	17 (41%)	13 (31%)	10 (37%)	4 (31%)	3 (30%)
Wellbeing					
USD score 0≤3	19 (45%)	23 (55%)	15 (56%)	8 (62%)	7 (70%)
USD score 4≤6	2 (5%)	5 (12%)	3 (11%)	1 (8%)	0
USD score ≥7	3 (7%)	1 (2%)	0	0	0
Missings	18 (43%)	13 (31%)	9 (33%)	4 (31%)	3 (30%)

Table 5: Symptom prevalence, symptom intensity and wellbeing

	Patients on combination therapy				
Symptom and symptom intensity	**Baseline (T=0) (N=6) N (%)**	**3 months (T=1) (N=6) N (%)**	**6 months (T=2) (N= 1) N (%)**	**9 months (T=3) (N= 1) N (%)**	**12 months (T=4) (N= 0) N (%)**
Anorexia					
USD score 0≤3	5 (83%)	3 (50%)	1 (100%)	1 (100%)	0
USD score 4≤6	1 (17%)	0	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Constipation					
USD score 0≤3	6 (100%)	3 (50%)	0	1 (100%)	0
USD score 4≤6	0	0	1 (100%)	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Diarrhea					
USD score 0≤3	6 (100%)	3 (50%)	1 (100%)	1 (100%)	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Blood/mucus stool					
USD score 0≤3	6 (100%)	3 (50%)	1 (100%)	1 (100%)	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Abdominal pain					
USD score 0≤3	5 (83%)	3 (50%)	0	1 (100%)	0
USD score 4≤6	0	0	1 (100%)	0	0
USD score ≥7	0	0	0	0	0
Missings	1 (17%)	3 (50%)	0	0	0

Cough					
USD score 0≤3	6 (100%)	2 (33%)	1 (100%)	1 (100%)	0
USD score 4≤6	0	1 (17%)	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Visual changes					
USD score 0≤3	5 (83%)	3 (50%)	1 (100%)	1 (100%)	0
USD score 4≤6	1 (17%)	0	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Skin change					
USD score 0≤3	5 (83%)	3 (50%)	1 (100%)	1 (100%)	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	1 (17%)	0	0	0	0
Missings	0	3 (50%)	0	0	0
Rash					
USD score 0≤3	5 (83%)	3 (50%)	1 (100%)	0	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	1 (17%)	0	0	0	0
Missings	0	3 (50%)	0	1(100%)	0
Headache					
USD score 0≤3	6 (100%)	3 (50%)	0	1 (100%)	0
USD score 4≤6	0	0	1 (100%)	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Myalgia					
USD score 0≤3	5 (83%)	2 (33%)	1 (100%)	1 (100%)	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	0	1 (17%)	0	0	0
Missings	1 (17%)	3 (50%)	0	0	0
Arthralgia					
USD score 0≤3	6 (100%)	3 (50%)	1 (100%)	1 (100%)	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0

Tingling					
USD score 0≤3	5 (83%)	3 (50%)	1 (100%)	1(100%)	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	1 (17%)	0	0	0	0
Missings	0	3 (50%)	0	0	0
Pain					
USD score 0≤3	6 (100%)	2 (33%)	1 (100%)	1 (100%)	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	0	1 (17%)	0	0	0
Missings	0	3 (50%)	0	0	0
Sleeping problems					
USD score 0≤3	3 (50%)	2 (33%)	0	1 (100%)	0
USD score 4≤6	1 (17%)	1 (17%)	1 (100%)	0	0
USD score ≥7	2 (33%)	0	0	0	0
Missings	0	3 (50%)	0	0	0
Nausea					
USD score 0≤3	6 (100%)	3 (50%)	1 (100%)	1 (100%)	0
USD score 4≤6	0	0	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Dyspnea					
USD score 0≤3	6 (100%)	3 (50%)	0	1 (100%)	0
USD score 4≤6	0	0	1 (100%)	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Fatigue					
USD score 0≤3	2 (33%)	1 (17%)	0	1 (100%)	0
USD score 4≤6	3 (50%)	2 (33%)	0	0	0
USD score ≥7	1 (17%)	0	1 (100%)	0	0
Missings	0	3 (50%)	0	0	0
Anxiety					
USD score 0≤3	5 (83%)	3 (50%)	1 (100%)	1 (100%)	0
USD score 4≤6	1 (17%)	0	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0

Gloom					
USD score 0≤3	5 (83%)	2 (33%)	1 (100%)	1 (100%)	0
USD score 4≤6	1 (17%)	1 (17%)	0	0	0
USD score ≥7	0	0	0	0	0
Missings	0	3 (50%)	0	0	0
Inactivity					
USD score 0≤3	3 (50%)	1 (17%)	1 (100%)	1 (100%)	0
USD score 4≤6	2 (33%)	1 (17%)	0	0	0
USD score ≥7	1 (17%)	1 (17%)	0	0	0
Missings	0	3 (50%)	0	0	0
Wellbeing					
USD score 0≤3	2 (33%)	1 (17%)	0	1 (100%)	0
USD score 4≤6	4 (67%)	1 (17%)	1 (100%)	0	0
USD score ≥7	0	1 (17%)	0	0	0
Missings	0	3 (50%)	0	0	0

APPENDIX 2: USD IMMUNOTHERAPY

Sticker met patiëntgegevens

Utrecht Symptoom Dagboek (USD)

IMMUNOTHERAPIE

Datum ……/……./……..

Instructie

- Wilt u vóór uw bezoek aan uw verpleegkundige door middel van een cijfer aangeven hoe u zich op dit moment voelt of hoeveel last u ergens van heeft? Deze lijst wordt door de verpleegkundige met u besproken. U kunt uw antwoorden dan nader toe te lichten. Waar nodig en in overleg met u kunnen we de zorg bijstellen.
- Door het omcirkelen van het cijfer geeft u aan hoeveel last u had van de klacht toen deze het ergst was in de **periode tussen uw vorige bezoek aan de dagbehandeling en vandaag**; 0 = afwezigheid van de klacht of het gevoel; 10 = de slechtst denkbare situatie voor u, ofwel voortdurende aanwezigheid van klacht of het gevoel.
- Klachten of gevoelens die niet op de lijst voorkomen kunt u in de vrije regels toevoegen.

Ik heb de afgelopen periode (geef de hoogste score aan)

goede eetlust	0	1	2	3	4	5	6	7	8	9	10	geen eetlust
normaal ontlastingpatroon	0	1	2	3	4	5	6	7	8	9	10	erg verstoord ontlastingpatroon
geen diarree	0	1	2	3	4	5	6	7	8	9	10	erge diarree
geen bloed of slijm bij de ontlasting	0	1	2	3	4	5	6	7	8	9	10	veel bloed of slijm bij de ontlasting
geen buikpijn	0	1	2	3	4	5	6	7	8	9	10	veel buikpijn

geen last van hoesten	0	1	2	3	4	5	6	7	8	9	10	erge last van hoesten
geen oogklachten	0	1	2	3	4	5	6	7	8	9	10	erge oogklachten
geen rode huiduitslag	0	1	2	3	4	5	6	7	8	9	10	erge rode huiduitslag
geen jeuk	0	1	2	3	4	5	6	7	8	9	10	erge jeuk
geen hoofdpijn	0	1	2	3	4	5	6	7	8	9	10	erge hoofdpijn
geen spierpijn	0	1	2	3	4	5	6	7	8	9	10	erge spierpijn
geen gewrichtspijn	0	1	2	3	4	5	6	7	8	9	10	erge gewrichtspijn
geen doof of tintelend gevoel in armen/benen	0	1	2	3	4	5	6	7	8	9	10	erg doof of tintelend gevoel in armen/benen
geen pijn	0	1	2	3	4	5	6	7	8	9	10	erg veel pijn
geen slaapprobleem	0	1	2	3	4	5	6	7	8	9	10	erg groot slaapprobleem
Anders												
.....	0	1	2	3	4	5	6	7	8	9	10	.....
.....	0	1	2	3	4	5	6	7	8	9	10	.....

Ik voel me in de afgelopen periode (geef de hoogste score aan)

niet misselijk	0	1	2	3	4	5	6	7	8	9	10	erg misselijk
niet benauwd	0	1	2	3	4	5	6	7	8	9	10	erg benauwd

niet moe	0	1	2	3	4	5	6	7	8	9	10	erg moe
niet angstig	0	1	2	3	4	5	6	7	8	9	10	erg angstig
niet somber	0	1	2	3	4	5	6	7	8	9	10	erg somber
Anders												
…….	0	1	2	3	4	5	6	7	8	9	10	…….
…….	0	1	2	3	4	5	6	7	8	9	10	…….

Ik ben de afgelopen periode (geef de hoogste score aan)

actief	0	1	2	3	4	5	6	7	8	9	10	niet actief

Ik voel me de afgelopen periode (geef de hoogste score aan)

goed	0	1	2	3	4	5	6	7	8	9	10	erg slecht

In hoeverre beïnvloeden de bijwerkingen van de behandeling uw kwaliteit van leven?

helemaal niet	0	1	2	3	4	5	6	7	heel erg

Welke klacht(en) moet(en) wat u betreft als eerste aandacht krijgen?