# Health-related quality of life, emotional burden, and neurocognitive function in the first generation of metastatic melanoma survivors treated with pembrolizumab: a longitudinal pilot study

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**Health Related Quality of life, emotional burden and neurocognitive function in the first generation of metastatic melanoma survivors treated with pembrolizumab: a Longitudinal pilot study**

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**Purpose**: The aim of this study was to assess the evolution of health-related quality of Life (HRQoL), emotional burden and neurocognitive function in the first generation metastatic melanoma survivors treated with pembrolizumab.
**Methods**: Survivors were defined as patients who achieved a durable remission for at least 6 months after initiating pembrolizumab in a single-center observational study (*N*=141). A semi-structured interview was performed at baseline. Neurocognitive computerized testing and patient reported outcomes were collected at 4 time-points to assess HRQoL using the EORTC QLQ-C30 and the HADS to assess anxiety and depression.
**Results**: Out of 35 eligible patients, 25 were recruited and completed baseline assessment (18 female; median age: 58 years [range 28-86]; 24 completed the 1 year follow-up phase. Median time since diagnosis was 30 months (range 12-84); median time since initiation of pembrolizumab was 19 months (range 6-42). At all visits, survivors reported a significantly lower global HRQoL, lower physical, emotional, cognitive, role and social functioning compared to the European Mean of the healthy population. Fifteen patients (64%) had clinical levels of anxiety/depression at one time-point during follow-up. The clinical interview revealed that 12 patients (48%) suffered from Cancer-Related-Post-Traumatic-Stress disorder, of whom 7 (28%) developed transient suicidal ideation, 1 patient made a suicide attempt. Neurocognitive testing revealed cognitive impairment in 8 patients (32%)
**Conclusions**: Metastatic melanoma survivors, treated successfully with pembrolizumab, are at risk for suffering from emotional distress and neurocognitive impairment with a persistent impact on their HRQOL. Timely detection in order to offer tailored care is indicated.

***Key words:*** *cancer survivorship, quality of life, psychosocial outcome, melanoma, pembrolizumab, immunotherapy*

## Introduction

Cancer survivors are at risk of suffering from anxiety, depression, suicidal ideation, fear of recurrence existential problems, and neurocognitive dysfunction persisting after physical recovery from their disease [1]. These mental and neurocognitive symptoms are associated with delayed return to work, diminished activities of daily living, impaired family relationships and reduced quality of life [2, 3].

Since 2010, an increasing proportion of patients with advanced melanoma treated with immunotherapy and/or BRAF/MEK-inhibitors, achieve long-term survival. In particular, treatment with the PD-1 blocking monoclonal antibodies pembrolizumab and nivolumab has substantially improved the chance for survival without the necessity to indefinitely continue treatment [4, 5]. Moreover, an inflection point on the progression-free survival (PFS) curve for patients treated with pembrolizumab or nivolumab is observed between 6 and 9 months, with a substantially lower risk for being diagnosed with progression of disease after this time-point [6]. The five-year PFS-rate is in the order of 25% and it can be expected that the majority of these patients will be able to resume normal life. In the Keynote 002, is was found that HRQoL was better maintained with pembrolizumab than with chemotherapy during the acute treatment phase [7]However, until now there has been scarce information regarding the psychosocial outcome and the quality of life of metastatic melanoma survivors experiencing disease control following immune checkpoint blockade [8]. Most studies have been cross-sectional or retrospective in nature [9].

Previous studies focusing on melanoma survivorship were mainly survey-based, including patients with non-metastatic disease treated with adjuvant therapy [5]. Those studies reported diminished wellbeing, more distress and fear of recurrence compared to other cancer survivors [10]. This might be related to the necessity of continued self-examination, dermatological controls and reduced sun exposure. Higher anxiety levels and fear for recurrence can have an impact on the outcome as these are associated with avoidance behavior in relation to dermatological controls [11]. Melanoma is often associated with frequent relapses and traumatic disease related symptoms, such as rapidly growing and/or disfiguring skin metastases [12]. Moreover, the long term survival rates of patients responding to anti-PD1 therapy remain unknown as well as unanswered questions with regards to optimal duration of therapy and treatment guidelines in case of recurrence. Consequently patients are more likely to suffer from the uncertainty surrounding this new standard of care, leading to higher levels of fear of recurrence and emotional distress, such as coping difficulties, anxiety and depression [13]. This emotional distress and the related emotional burden of having cancer can impact psycho-social outcome, which refers to the emotional, social, professional and financial difficulties that cancer survivors can encounter.

Finally, chronic emotional distress itself provokes a dysregulation of inflammatory processes, which could potentially influence the microenvironment of the tumor and alter the immune response through immunosuppressive pathways [14, 15] . Stress, but also cancer, radiotherapy and surgery activates pro-inflammatory cytokines such as Interleukin-1, Interferon alpha (IFNα), and Tumor Necrosis Factor (TNFα). These pro-inflammatory cytokines influence neural signaling, which causes dysregulation of inflammatory responses through the hypothalamic pituitary axis (e.g. regulation of glucocorticoids with the inflammatory signaling molecules NFkB and p38 mitogen activated protein kinase) [16]. Preclinical models indicate that stress can enhances cancer progression in mice models [17]. That treatment outcomes could potentially be improved by offering distress-reducing tailored psycho-social care, is an additional incentive for studying this advanced melanoma survivor population, especially following successful treatment with PD-1 blocking monoclonal antibodies such as pembrolizumab and nivolumab.

The purpose of this prospective longitudinal pilot study was to investigate the Health Related Quality of Life, the emotional burden and the neurocognitive outcome in metastatic melanoma survivors treated with pembrolizumab in a single-institution observational trial, in order to provide a foundation for adapted psychosocial care to this growing population of cancer survivors.

# Methods

This is a single-center prospective observational sub-study of an ongoing clinical study (ClinicalTrials.gov Identifier: NCT02673970) on "Biomarkers for the activity of immune checkpoint inhibitor therapy in patients with advanced melanoma", approved by the Ethical Committee (EC) of the Universitair Ziekenhuis Brussel in 2014. Study results have been published previously [4]. The sub-study was approved by the EC in April 2016.

## Study population

Melanoma patients with unresectable AJCC stage III or IV disease were eligible for this sub-study if they were on pembrolizumab treatment for at least 6 months and free from progression at their latest follow-up (according to iRECIST tumor response criteria). Patients had to be older than 18 years, physically and mentally capable to fill in the questionnaires in Dutch, French or English and to perform the computer assisted neurocognitive testing. Patients with cognitive impairment were excluded.

## Procedures

Patients were invited to participate in the sub-study between November 2016 and May 2017 at the time of their oncological follow-up visit. Eligible patients were identified within the ongoing parental study and were invited to participate at the moment of their planned oncological visit. Baseline assessments were defined as the first assessment conducted at the convenience of each patient. The duration of the baseline assessment took approximately 2 hours and consisted of a clinical interview (60 minutes), cognitive testing (40 minutes) and filling in the questionnaires (20 minutes). From this time-point, subsequent assessments were planned every 3, 4 or 6 months in accordance with the frequency of the oncological follow-up visits as defined in the protocol of the parental observational study. Frequency of assessments varied in function of the time to remission, which implied that not all patients were evaluated at time-point 1 and 3. All eligible patients were presumed to have an assessment at baseline (T0), at 6 months (T2) and at 1 year follow up (T4).
All assessments were conducted at the hospital, after each oncological follow-up visit. To avoid bias related to the distress of the oncological control visit, all patients had already received the results of their oncological assessments. All questionnaires were checked for missing responses during the time of the neurocognitive assessment. Patients were asked to fill in the missing items, to avoid bias due to missing data. Additional clinical data on disease staging, ECOG, previous received treatments were collected from the parental prospective study. Socio-demographic data, sleep disturbances, physical activity and psychiatric history were collected using a generic questionnaire developed for this sub-study.

## Materials and data collection

### Patient reported outcomes

The Hospitalization Anxiety and Depression Scale (HADS) is a 14 item self-report instrument, including 7 items for anxiety and 7 items for depression on a 4 point Likert scale [18]. The HADS has been validated in Dutch and French [15, 19, 20]. A cut off score of $\geq 8$ has been validated as clinically important to assess emotional distress in the oncological setting [21]. A cut-off score >11 suggest a high probability of the presence of clinical depression. Internal consistency of the items of both scales is consistently very good ($.81 < \alpha < .94$ for anxiety and $.82 < \alpha < .88$ for depression).

The EORTC Quality of Life Questionnaire-C30 (EORTC QLQ-C30) is a patient reported outcome that assesses HRQoL in cancer patients [22]. The EORTC QLQ-C30 is composed of 30 items, consisting of 5 functional dimensions (physical, emotional, role, cognitive, and social functioning), 9 symptomatic

dimensions (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact), which are each scored on a 4 point Likert scale and one dimension of global HRQoL, measured by 2 items, each scored on a 7-point Likert scale. A higher score on the functional dimensions indicates better functioning, while a higher score on the symptom dimensions indicates more symptom burden. According to the guidelines, a linear transformation is used to standardize the raw scores from 0 to 100. Differences in scores of more than 10 points are considered as clinically relevant [23]. The EORTC QLQ C-30 has been validated in French and Dutch [24].

The Fatigue Severity Scale (FSS) is a 9 item self-report instrument, on a 7 point Likert scale with a cut off score of $\geq 4$ indicating moderate fatigue [25]. The FSS has been validated in Dutch, French and in the oncological setting [26-28]. Internal consistency of the items is consistently very good ($.93 < \alpha < .97$).

### Neurocognitive assessment

Neurocognitive function was assessed, using the Cogstate computerized battery of tests, validated in oncological settings and evaluating processing speed (Detection test; DET), attention (Identification test; IDN), verbal memory (International Shopping List; ISL and delayed ISL; ISLR), working memory (One Back test; ONB) and executive function (Groton Maze Learning Task; GMLT [29, 30]. For each patient, performance on each test was standardized using age matched normative data. The Cogstate normative dataset represents data from a global healthy population of adults, clustered into age bins across the lifespan [31, 32]. The normative data is collapsed across geographic regions given the evidence to suggest that there is sound cross-cultural equivalence of performance on tests within the test battery [33] [34]. The classification of clinically meaningful impairment on an individual test was classified if a subject obtained a z-score $\leq -1.00$. This value was selected given its application in terms of clinical importance, where it is used currently to assist with decisions in clinical settings [35]. Classification of cognitive impairment also requires consideration of the number of tests administered and the number of tests for which impairment has been classified. Given the likelihood of a classification of impairment occurring by chance alone increases as the number of tests administered increases, overall impairment should be classified only when there is evidence of impairment on approximately 50% of tests in the battery [35] [36]. As such impairment on a single test was classified when performance was lower than 1 standard deviation below normal age appropriate mean. For an individual, cognitive impairment was classified when abnormal performance occurred on at least 3 tests of the 7 in the battery. Following composite cognitive functions were defined: memory processing speed compound (IDN, DET), memory compound (ISL, ISLR, ONB) and executive function compound (GMLT, ONB).

### Interview and psychiatric examination

A semi-structured clinical interview was conducted at baseline by the first author, an experienced qualified psychiatrist with 20 years of experience in psychiatry and psycho-oncology [37]. Interviews were performed in Dutch, English or French and started with the open ended question on the patient's perception of how and by whom the diagnosis of metastatic melanoma was communicated and what emotions the patients felt at that moment. Thereafter a structured standard psychiatric examination based on DSM-IV-R-clinical version (SCID-IV-CV) was performed, investigating appearances, speech, mood, cognition, suicidal thoughts. Notes were filled in on a standardized form. The purpose of this clinical interview was to have additional clinical information to the patient reported outcomes, as the predicted sample size was too small to detect with sufficient statistical power differences in the prevalence rates to the normal population. Moreover up until now, no questionnaires have been validated in the metastatic melanoma survivor population, nor within the field of immune therapy [5].

### Data analysis

Statistical analysis was performed using R-Studio v3.5.1 and SPSS v25 with an alpha level of .05 two-sided. Norm based data of the EORTC QLQ_C30 from the European Healthy population [38] were compared with the HRQoL outcomes of the study population. Comparison with norm based data of HRQoL was performed using one sample t-test. Internal reliability of the items of the patient reported outcomes is measured by Cronbach's Alpha test**.**

# Results

## Study population

Out of a total of 141 patients surveyed, 30 patients had died of progression of metastatic melanoma, 5 patients died of a non-melanoma related cause, and 71 patients had previously progressed on pembrolizumab (Figure 1). Thirty five patients were identified as metastatic melanoma survivors as defined in this protocol and invited to participate in this sub-study. Twenty-five patients consented to participate and were recruited between 16/11/2016 and 01/05/2017. One patient declined to participate, 2 were lost to follow-up and 7 patients were unable to fill in the patient reported outcomes: 2 for linguistic reasons and 5 due to neurocognitive impairment.
Patient characteristics are summarized in Table 1. Twenty patients achieved a complete response, and 5 were free from progression for at least 6 months. Thirteen patients were no longer on pembrolizumab at study entry, with a median time after stopping treatment of 8 months (range 1-19). At the end of the study only 2 patients remained on pembrolizumab, time of stopping pembrolizumab for each patient is described in table 3. Correlations between the duration of pembrolizumab treatment, the time of start and stop pembrolizumab to baseline and respectively anxiety, depression (HADS), global quality of life (EORTC QLQ-C30) and fatigue (FSS) were non-significant, suggesting consistency of the baseline measure. We computed correlations between the time of start of PEMBRO to baseline assessments (T0) and the outcome measures (namely anxiety, depression, global quality of life and fatigue) on the one hand and time to remission of disease to T0 and the same outcome measures on the other hand. All correlations were non-significant (r^2 between .0001 and .058), suggesting consistency of the baseline measure.

As anticipated, not all patients were evaluated at each time-point: at time-point 1, only 18 patients had an assessment: 3 patients missed their assessment and for 4 patients control visits were planned every 6 months. At time-point 4 only 6 patients were assessed, this was due to changes in clinical practice, were only patients at high risk of recurrence of disease had control visit every 3 months, and thus had an additional control visit. At time-point 2 and 4, 24 patients had their planned assessment: one patient was not able to continue the assessments, due to degradation of the medical condition in relation to recurrence of disease at T4 (Figure 2).

Figure 1.

Table 1.

Figure 2.

## Toxicity

An overview of remaining physical sequels is presented in table 3. Twelve patients had unresolved irAE, 5 patients had vitiligo (grade 1-2), 3 patients suffered from persisting fatigue (grade 1-2) and 5 patients remained on hormone substitution. Following physical sequels were related to the disease or adjuvant therapy: 2 patients suffered from lymphedema (grade 2), 3 patients from hemiparesis due to radiation necrosis of the brain, one had a splenectomy and 1 patient an aseptic necrosis of the femoral head.

## Health related quality of life

At baseline, mean EORTC QLQ-C30 Global Score was significantly lower than the European Mean of the healthy population [38] and remained low at each time-point. At the end of the survey, 8 patients had a clinical relevant improvement (>10 points), and 6 patients clinically worsened (> 10 points). Mean scores for physical, role, emotional, cognitive and social functioning scales were significantly lower at all time-points, compared to the healthy population. Mean, indicating greater impairment. Survivors had a significantly higher symptom level of fatigue, pain, insomnia at all time-points. Financial difficulties were higher at baseline, but thereafter no differences were found compared to healthy population Mean. Table 2 gives a summary of the mean scores on the functional and symptom scales compared to the European mean.

Table 2**.**

## Anxiety and depression

According to the HADS (cut off = 8), anxiety was more prominent compared to depression. Mean scores remained below the cut-off score. However, at some time-point, 15 patients suffered from anxiety, of whom 10 with co-morbid clinically relevant depressive symptoms, only 1 patient suffered from depressive symptoms without anxiety. Eight patients suffered from severe anxiety (≥11), fluctuating over time. Three patients had persistent high scores (≥11) on both anxiety and depression subscales. Anxiety, depressive symptoms according to the HADS, fatigue (FSS), global HRQOL, emotional, social, cognitive and physical functioning according to the EORTC QLQ-C30 were highly correlated. A summary of these results can be found in Table 3. Descriptive statistics and correlations between the main variables are available in the supplementary data.

Table 3.

## Semi-structured clinical interview

The clinical interview revealed that all survivors reported fear of cancer recurrence (FCR) of whom 14 (56%) worried daily about their disease. Thirteen patients (52%) received a message of no hope at diagnosis of metastatic disease which had a persistent psychological impact, characterized by existential problems and high levels of emotional distress according to the HADS, 4 patients identified the announcement of the diagnosis as life threatening stressor (table 2). Eight patients (32%) reported worrying about their family; 5 patients (20%) relational problems and 10 reported (40%) financial problems related to the disease. According to SCID-IV-CV twelve patients (48%) suffered from cancer related post-traumatic stress disorder of whom 7 developed transient suicidal ideation, 1 female patient made a suicide attempt. One patient developed panic disorder with agoraphobia, with an onset at the day of receiving the diagnosis of metastatic disease. No patient suffered from a clinical major depressive disorder. Table 3 summarizes the AJCC stage, the immune related adverse events (irAE), and the physical sequels of the irAE and/or adjuvant therapy in relation to neurocognitive impairment, suicidal ideation, and emotional burden.

Table 4.

## Fatigue

Mean fatigue scores remained below the cut-off for the Fatigue Severity Scale. At baseline, 11 patients (42%) had elevated scores on the Fatigue Severity Scale of whom 9 patients were still on pembrolizumab. Fatigue varied for each patient from time-point to time-point: 15 patients (60%)

suffered from fatigue during at least one follow up visit. The number of patients who suffered from fatigue is summarized in Table 3.

### Neurocognitive testing

Aside from Processing Speed at Baseline, group mean impairment did not exceed $z \leq -1.00$ for any test (Table 5). At baseline five of the 25 patients (20%) had overall cognitive impairment, of whom 4 were still on treatment. During the survey 3 patients had overall impairment, on at least 2 time-points and 8 patients (32%) on at least 1 time-point. Only 2 of the 5 patients with a history of brain metastasis had overall impairment (Table 5 ) At the $z \leq -1.00$ cut-off, 10 of the 25 patients (40%) were impaired on 2 or more tests. Performance was relatively stable across the five assessments (Time 0 to Time 4) across each neurocognitive composite. Improvement was evident between Time 0 and Time 1 on Processing Speed, although performance was stable hereafter. Figure 3 illustrates the longitudinal evolution of the computerized neurocognitive testing.

No significant correlations were found between memory, processing speed and executive function and respectively fatigue (FSS), anxiety, depression (HADS), subjective cognitive function (EORTC QLQ-C30) and Global HRQOL.

Table 5

Figure 3

## Discussion

To the best of our knowledge, this is the first study exploring HRQOL, psychosocial and neurocognitive outcome in survivors of metastatic melanoma treated with the PD-1 blocking monoclonal antibody pembrolizumab. The main results revealed that the majority of survivors (68%) have persistent reduced global HRQOL which remained impaired during follow-up for a majority (58%) of them. They reported diminished physical, role, social, emotional and neurocognitive functioning, as well as a higher symptom burden of insomnia, fatigue and more financial difficulties compared to the healthy population, during the first 2 years after achieving remission of disease. Reduced physical and social functioning might be related to the important remaining physical sequels due to the irAE and adjuvant therapy. Reduced physical, social and physical role functioning was also found in a recent survey by O'Reilly, investing HRQOL in metastatic melanoma survivors treated with immune checkpoint inhibitors based the SF-36 (a non-cancer specific questionnaire).

The psychiatric interview revealed that approximately half of the patients had cancer-related post-traumatic stress disorder (PTSD), which in some (28 %) was associated with brief moments of acute suicidal ideation or a strong wish to die. The frequent prior recurrences, the experiences related to rapid evolving clinical symptoms associated with metastasis, the uncertainty related to the novel treatment, the physical sequels of prior adjuvant treatment for metastatic disease, as well as unexpected severe grade III/IV irAE, were identified as traumatic events (Table 4). PTSD is an anxiety disorder, characterized by a state of hyper arousal (irritability, insomnia and anxiety), intrusive thoughts (fear of recurrence, depressive symptoms and concentration problems) and avoidance behavior (avoidance of dermatological controls, decreased sun protection) [39, 40]. In its early phase, PTSD can be successfully treated with trauma-oriented therapy, and if necessary antidepressants. Early detection might reduce avoidance behavior, diminish distress and suicidal ideation, which could have a potential impact on treatment outcome. If untreated, PTSD can lead to co-morbid depression, anxiety disorders, sleep disorders and substance abuse, with a major impact on quality of life, return to work and psychosocial outcome [40]. Identifying traumatic events during the disease phase, can prevent the onset of PTSD. A majority of melanoma survivors suffer from fear of cancer recurrence which was associated with high

levels of uncertainty about the possible outcome of the novel treatment they received and related to the high number of relapses before receiving pembrolizumab. These findings are in accordance with previous published studies [13, 41]. Despite the existence of melanoma specific tools to reduce fear of recurrence, there is a need to develop specific tools in the therapeutic field of immune checkpoint inhibition, which takes into account the specific traumatic aspects of the disease process, the immune related adverse events and the remaining items of uncertainty in this new therapeutic field [42].

Clinically important increases in anxiety and depression, during at least time-point, occurred in the majority (60 %) of patients. However, mean scores of the HADS remained below the threshold for classification of depressive disorder, which can be explained by the high variability between patients in their symptom severity.

Mean scores on the cognitive tests remained within the normal range and were not correlated with fatigue, anxiety or subjective cognitive impairment. However, five patients were classified at baseline as having neurocognitive impairment of whom 4 were still on pembrolizumab. These findings, as well as the well-known interaction between the immune system, inflammation, cancer, and cognitive function [16] suggest that further investigation of cognitive function, using objective testing is of interest. It was recently found that neuronal auto-antibodies might play a role in cognitive impairment in melanoma patients [43].

Our study is limited by the small number of patients. Given the sample specificity (all participants had to achieve a complete remission of disease in remission on PEMBRO) of this pilot study, we had a small number of respondents. Therefore this study might lack power and consequently fail to detect other possible effects.
In absence of a control group, normative data were used to assess HRQOL, neurocognitive function and anxiety and depression. Another limitation are the important number of missing data at 2 time-points in the study, and the different time-points of the baseline assessment since start PEMBRO treatment. This needs to be taken into account in the interpretation of the results and further studies are necessary to confirm our findings.
The strengths of the study are the longitudinal, prospective study design and the additional qualitative information. In absence of validated scales in this new therapeutic field, the additional clinical interview is of major interest. An additional strength is that all patients achieved durable responses on pembrolizumab, which might reduce confounding factors, related to differences in pharmacological and immunological characteristics between different types of immune therapy and BRAF/MEK- inhibitors.

Our results indicate that advanced melanoma survivors treated with pembrolizumab, and likely also with other immune checkpoint inhibitors, are at risk for suffering from severe emotional distress and neurocognitive dysfunction with impact on their quality of life, physical, social, cognitive and role functioning, after achieving remission, which remains unchanged during the first two years of survivorship. This preliminary results point out the need for developing specific questionnaires in order to timely detect physical, social, financial, cognitive and emotional burden including suicidal ideation. Psycho-educational programs, neurocognitive training, mindfulness and physical exercise have already demonstrated to reduce distress in cancer survivors, but need further investigation in this setting of patients successfully treated with immunotherapy for metastatic melanoma [42, 44, 45].

A better understanding of the complex relationships between the immune system, immune related adverse events, the tumor microenvironment, cognition and emotional distress might lead to a better treatment outcome. In addition, as novel treatments have become part of our standard of care in the adjuvant setting, this patient population also deserves attention with regards to their quality of life and psychosocial and neurocognitive outcome.

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**Author contributions:** A. Rogiers, conceived and performed the study design, performed the data collection, developed the manuscript, the data analysis and the data interpretation; Christophe Leys commented on the manuscript, performed the data analysis, the statistical analysis and took part in the interpretation of the data; Jennifer De Cremer assisted on the data collection and commented on the manuscript. Gil Awada assisted on the data collection and commented on the manuscript. Adrian Schembri assisted in the study design, commented on the manuscript and assisted to the data analysis; Peter Theuns commented on the manuscript; Mark de Ridder commented on the manuscript; Bart Neyns assisted in the study design, took part in the data interpretation and developed and commented the manuscript.

**Data availability:** Data and material is available upon request from the corresponding author

## Compliance with ethical standards

### Ethics approval and consent to participate

The study (ClinicalTrials.gov Identifier: NCT02673970) on "Biomarkers for the activity of immune checkpoint inhibitor therapy in patients with advanced melanoma", was approved by the Ethical Committee (EC) of the Universitair Ziekenhuis Brussel in 2014, and the sub-study in April 2016.

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