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Symptom Experience of Patients with Advanced Melanoma Undergoing Immune Checkpoint Inhibitor Therapy

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SYMPTOM EXPERIENCE OF PATIENTS WITH ADVANCED MELANOMA UNDERGOING IMMUNE CHECKPOINT INHIBITOR THERAPY

A DISSERTATION

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SCHOOL OF NURSING

BY

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Date

To the Dean for the School of Nursing:

I am submitting a dissertation written by Natalie Jackson-Carroll and entitled "Symptom Experience of Patients with Advanced Melanoma Undergoing Immune Checkpoint Inhibitor Therapy." I have examined the final copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.

Meagan Whisenant
Meagan Whisenant, PhD, APRN, Committee Chair

We have read this dissertation

and recommend its acceptance:

MD, MAPH Committee member

PhD

PhD.

Accepted

Dean for the School of Nursing

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Symptom Experience of Patients with Advanced Melanoma Undergoing Immune Checkpoint Inhibitor Therapy

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Abstract

Background: Immune checkpoint inhibitors (ICIs) are novel therapeutic agents utilized in the management of advanced melanoma. Though generally well-tolerated, patients receiving ICIs experience treatment-related toxicities at varying onset and intensity. Assessment and evaluation of these toxicities and their impact on a quality of life is essential to comprehensive cancer care. Patient-reported outcomes (PRO) contribute vital data to a clinical assessment, supporting clinicians in their ability to improve outcomes. To date, there is no melanoma-specific or ICI-specific PRO measure of symptom burden available.

Purpose: The purpose of this study was to describe the symptom experience from the patient's perspective and how it relates to the quality of life among patients undergoing ICIs for advanced melanoma across the treatment trajectory. In addition, this study assessed the concordance between symptoms communicated to clinicians during a follow-up visit and those reported via PRO instruments.

Methods: This was a cross-sectional, mixed-methods evaluation of the symptom experience of patients with advanced melanoma within their first year of ICI therapy. Participants completed two PRO instruments: the FACT-M and a

modified version of the MDASI. The clinical review of systems was captured from the electronic health record following the visit in which the PRO instruments were completed to assess degree of matching. A subset of participants completed semi-structured, qualitative interviews to enrich the quantitative data. Interpretive description informed the inductive and iterative analysis approach.

Results: All 60 participants reported at least one symptom on the PRO instruments. Most commonly reported on the modified MDASI were lack of energy (N=43, 72%), fatigue (n=42, 71%), feeling drowsy (n=35, 60%), joint stiffness/soreness (n=34, 57%), disturbed sleep (n=33, 56%), dry mouth (n=32, 53%), and itching (n=30, 50%). Most commonly reported on the FACT-M were fatigue (n=49, 82%), lack of energy (n=46, 77%), worry that the disease would get worse (n=38, 63%), worry about dying (n=32, 54%), and feeling sad (n=32, 54%). More than 50% of participants reported interference with working (n=32, 53%) and general activity (n=33, 55%). Participants reported three or more symptoms on the PRO instruments when compared to the number of symptoms documented in the clinician ROS in the EHR. The participants (n=19) who completed the qualitative interviews had a heterogenous experience of ICI and melanoma-related symptoms. The most commonly reported symptoms in qualitative interviews included distress (n= 16, 84%), fatigue (n=13, 68%), and rash (n=10, 53%). Uncertainty was a pervasive theme (n=13, 68%), despite the majority having positive thoughts about ICI therapy (n=11, 58%) and expectations of the success of therapy (n=10, 53%).

Conclusion: The physical and emotional burden of a melanoma diagnosis and related therapy and the uncertainty of outcomes are common themes described by patients. Communication surrounding the diagnosis, prognosis, treatment options, and outcomes needs to be clear and acknowledge that there are unknowns. Providers may benefit from utilizing a validated PRO instrument to evaluate and understand patients' symptom experiences while undergoing ICI therapy. Further research is needed to finalize a melanoma ICI-specific instrument.

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Summary of Study

Development of Idea to Proposal

As a provider in the melanoma clinic caring for patients with advanced melanoma while undergoing immune checkpoint inhibitor (ICI) therapy, the Principal Investigator (PI) noticed little consistency in clinical documentation regarding the presence and severity of toxicities. While the Common Terminology Criteria for Adverse Events (CTCAE) was considered as a possible measure for capturing symptoms, it is already available and not currently used in clinics. A brief verbal poll with the advanced practice providers at the melanoma center where the study was completed for reasons, they were (1) it is cumbersome to use, (2) limited experience using it clinically, (3) it is not easily accessed in the electronic health record so it is not used. The PI further observed that follow-up on a patient regarding a previous adverse event was fragmented, especially when providers did not adequately document the adverse event experience in the medical record. Use of a patient-reported outcomes (PRO) measure for systematic and valid measurement of symptoms related to adverse events was identified as a possible solution that would support communication and continuity of care.

Two PRO instruments are commonly used for assessing symptoms and quality of life in patients living with melanoma: the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Melanoma (EORTC QLQ-MEL 38). Clinical trials that led to the FDA approval of the current

ICI therapy options utilized a combination of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30 questions (EORTC QLQ- C30), EuroQol-5D (EQ-5D; (Coens et al., 2017; Larkin et al., 2018; Long et al., 2016; Petrella et al., 2017; Revicki et al., 2012; Schadendorf et al., 2016; Weber et al., 2017). One study included the EORTC-OLQ-C30, the EQ-5D, and the Work Productivity and Activity Impairment Questionnaire: General Health (Schadendorf et al., 2017). A systematic review by the PI explored the use of PRO measures in research outside of clinical trials. Some studies included generic measures such as the EORTC QLQ-30, EQ-5D, the Medical Outcomes Study 36-Item Short Form Health Survey (MOS-SF-36), the Functional Assessment of Cancer Therapy- General (FACT-G), or the Edmonton Symptom Assessment Scale (ESAS). Others included a few disease- or symptom-specific measures such as the FACT-M, Multidimensional Fatigue Inventory (MFI), Hospital and Anxiety and Depression Scale (HADS), Fatigue Severity Scale (FSS), Comprehensive Score for Financial Toxicity (COST), Impact of Event Scale - Revised (IESR), National Comprehensive Cancer Network Distress Thermometer (NCCN DT). The MD Anderson Symptom Inventory (MDASI) is a symptom assessment survey with evidence of validity and reliability in patients with cancer (Cleeland et al., 2000). Modules can be developed to assess specific oncology patient populations using a symptom item library (Cleeland et al., 2000).

After discussion with melanoma department experts, it was agreed to proceed with the FACT-M and use the MDASI symptom library to create a

modified version of the MDASI that could potentially capture the ICI experience and symptom burden of patients with advanced melanoma. An existing umbrella protocol approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center (BS99-094; PI: Xin Shelly Wang) allows for the evaluation of the symptom burden of patients with cancer undergoing different therapies for describing the symptom burden and supporting development of disease- and treatment-specific PRO measures. It was discussed and agreed that the PI would open a sub-study under the BS99-094 protocol and assess the unique experience of patients with advanced melanoma undergoing ICI therapy. The Committee for Protection of Human Subjects at UTHealth Houston agreed to rely on the MD Anderson IRB for the research activities for this project.

Implementation of the Study

The approved consent (Appendix A) for protocol BS99-094 was utilized for this study. The PI met with Darcy Ponce, an expert in use of Research Electronic Data Capture (REDCap, Harris et al., 2009, 2019). Citations for capturing PRO data and the necessary demographic information in the REDCap database were created (Appendix B). The PI met with three experts in melanoma and symptoms from immune checkpoint inhibitors to create the modified MDASI. The MDASI symptom library was provided, and if at least two experts voted on an item, it was included in the modified MDASI for this study. A presentation was given by the PI to the melanoma medical department to explain the specific aims and inclusion criteria and obtained permission to approach a potential participant with the option to participate. The first patient was enrolled on 09/06/2022, and the final

patient was enrolled on 12/15/2022. As patients were enrolled, the PI captured demographic and clinical data on an excel spreadsheet (Appendix C) to ensure a diversity of patient perspectives and experiences were captured, as planned in the Dissertation Proposal, such as age, race, and time on ICI therapy. The first qualitative interview was completed on 9/08/2022, and the final interview was conducted on 02/02/2023. Waiting this time allowed the PI to capture data from potentially the first and last enrollee, though not all patients were interested in completing the interview.

Data Collection

There were 65 patients enrolled, but only 60 completed the modified version of the MDASI and the FACT-M and were included in the analysis. While completing the PRO instruments, a participant offered their opinion about the questions within the instruments. It was decided that more data regarding this important insight should be captured and the question, “Do you feel the surveys you just completed adequately captured your treatment experience?” was added and completed by 51 participants of the study. For the semi-structured interviews, there were no adjustments made to the questions on the guide. The PI did not identify any unanticipated barriers to recruiting, enrolling, and completing data collection. Participants appeared engaged in the study, and the PI was able to enroll the minimum diversity goals as planned, other than race (Appendix D). It was anticipated that diversity of race could occur and the barrier to enrolling participants that were not White, was limited diversity of the patients scheduled in clinics who were on active therapy. Clinical, demographic, and

review of systems (ROS) data were extracted from the medical record by the PI into RedCap. The PI created the Degree of Matching excel data (Appendix E) for ease of evaluation of the extracted ROS data.

Data Analysis

Quantitative

With the assistance of Mr. Stanley Cron, data were cleaned and uploaded into SPSS Version 29.0.0 (*IBM SPSS Statistics*, 2020). The PRO instruments were scored, per the developer instructions. Based on a suggestion from Dr. Tawbi, a sensitivity analysis to support the categories for age and treatment type was completed. For age, three categories were derived: (1) <50 years, 50-65 years, 65 years and older, (2) over or under 65 years, as this is prevalent in melanoma studies, and (3) above and below the median age of the participants (61.4 years). Treatment type was divided as (1) monotherapy, combination therapy, or clinical trials and (2) monotherapy or combination therapy. A few participants were categorized into potentially unique categories due to the therapy combination ipilimumab + nivolumab. Participants who start a combination and then proceed with single-agent Nivolumab could be different than those who begin single-agent or those who remain on combination therapy such as nivolumab plus relatlimab. It was tested to see if outcomes were impacted by placing each participant in the single agent category versus all in the combination nivolumab + ipilimumab. Per the sensitivity analysis, there were no statistical differences; therefore, participants were categorized as single-agent Nivolumab, the regimen they were receiving at time of PRO measure completion.

Three participants were enrolled in a blinded clinical trial of adjuvant nivolumab versus adjuvant nivolumab plus relatlimab. It was decided to exclude data collected from these three participants in the final analysis and only evaluate data from the 57 participants we could confidently label.

As the data were reviewed and analyzed with SPSS software, the outputs were examined for consistency with the raw data. There were a few unique findings compared to the existing evidence-base, such as the fact that all participants documented symptoms on the PRO measures and the number of emotional symptoms and burden disclosed in this sample. There were also findings supporting the current literature in that some participants reported very mild symptoms and minimal impact on health-related quality of life (HRQoL).

Qualitative

Once the patient agreed to participate, the interview was scheduled and completed at a mutually agreed upon time. The interviews were completed over the phone, on speaker, and recorded with the knowledge and permission of each patient. Each interview was guided by the interview questions created with MW to also comply with the BS99-094 requirements. The recorded audio file was then uploaded to Adept Word Management (Adept, 2022) for professional transcription. Transcripts were received, reviewed and edited by the PI while listening to the interview audio recordings, and any errors were corrected. The transcribed documents were then uploaded into MAXQDA qualitative software version 22 (VERBI Software, 2021) for coding and to evaluate themes.

The PI initially coded the first three transcripts and sent them to Dr. Whisenant for evaluation and guidance. The subsequent discussion and clarification of being specific and slightly generic with the themes guided the rest of the coding of the transcribed interviews. Once all transcripts had been read and codes identified, it was decided first to document all the symptoms and words (Appendix F) used to describe interference in the transcribed interviews. Step two involved combining these words or phrases into broader categories. Going through each transcript and fine-tuning these categories was an iterative process, but specific themes, such as “distress”, became apparent. After this, other themes were easier to label and explain, such as “navigating the healthcare system.” There were four participants with whom the PI discussed the resulting themes and symptoms, providing examples, and these participants validated the findings.

The Symptom Experience of Patients with Advanced Melanoma Undergoing Immune Checkpoint Inhibitor (ICI) Therapy

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Dissertation Research Proposal

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Abstract

The expanded use of immune checkpoint inhibitors (ICIs) in cancer care has highlighted the frequency of immune-related adverse events (irAEs). irAEs can be permanent and are potentially life-threatening if not diagnosed and managed (Brahmer et al., 2018; Thompson et al., 2020). The range in severity of grade, onset, and duration of these events is reported with high variability, making it difficult to provide an anticipated pattern of expected irAEs during therapy (Chan & Bass, 2020). Unfortunately, providers can underestimate the symptom severity and frequency experienced by patients with cancer (Atkinson et al., 2016; Basch et al., 2009; Laugsand et al., 2010). Obtaining Patient-reported outcomes (PROs) data during the care of patients with cancer while receiving treatment is associated with improved quality of life (QOL) and overall survival (Basch et al., 2017; Husson et al., 2020). There is no current PRO instrument that has been validated in patients with advanced melanoma undergoing ICI. There is a *critical need* for a description from the patient perspective and a reliable measure of the symptom experience, specific to patients with melanoma receiving ICI. Early detection of toxicity allows for swifter management and potentially reduces the long-term negative impact on QOL. It is essential to improve outcomes by capturing the patient perspective of their symptoms, current management strategies, and related impairments in functioning and QOL while receiving ICIs for melanoma. The *long-term goal* is to develop instruments that capture and measure the ICI experience to evaluate the feasibility and benefit of interventions for ICI toxicities. Specific aim 1 is to

describe the symptom burden and its relationship with QOL for patients undergoing ICIs for their advanced melanoma across the treatment trajectory. Specific aim 2 is to evaluate the concordance between symptoms communicated during a follow-up visit and reported via PRO measure. Specific aim 3 is to explore the patient experience while receiving ICIs for melanoma using a qualitative approach via patient interviews. Methods: This is a mixed-methods observational study of 60 participants with advanced melanoma undergoing ICI therapy. Subjects will complete the modified MD Anderson Symptom Inventory (MDASI) and the Functional Assessment of Cancer Therapy- Melanoma (FACT-M). A subset (approximately n= 20) of the 60 will complete a semi-structured qualitative interview to explore their ICI therapy experience. Conclusion: To our knowledge, this is the first study to assess ICI symptoms utilizing the modified MDASI in patients with advanced melanoma undergoing ICI. Completing qualitative interviews to verify the experience has been accurately captured using existing measures is also novel in this population. The knowledge gained in this study will lay the foundation for future work to improve symptom assessment, management strategies, and outcomes for patients undergoing ICI therapy.

Specific Aims

Melanoma is the deadliest skin cancer, with an estimated 106,110 new cases of melanoma in 2021 and 7,180 deaths (*Melanoma of the Skin - Cancer Stat Facts*, n.d.). The 5-year survival for melanoma is now 93.37%, with almost 1.245 million people living with melanoma in the United States in 2017. Immune checkpoint inhibitors (ICIs) have improved outcomes for those with advanced melanoma, increasing long-term durable control from 10% up to almost 50% (Carlino et al., 2021). The negative impact of ICIs includes immune-related adverse events (irAEs), such as fatigue, colitis, pneumonitis, and endocrinopathies, which occur in up to 90% of patients (Thompson et al., 2020). The toxicities range in onset, intensity (Grade I-V), and duration of these events are reported with high variability making it difficult to provide an anticipated pattern of expected irAEs during therapy (Chan & Bass, 2020).

Early detection of irAEs and prompt intervention with immune suppression and/or immunomodulatory strategies are essential to provide the best patient outcomes possible (Puzanov et al., 2017; Thompson et al., 2020). The patient report of frequency and severity of disease- and treatment-related symptoms has a poor to moderate association with symptoms and toxicities measured by clinicians in cancer care (Atkinson et al., 2016; Basch et al., 2009; Laugsand et al., 2010). Patient-reported outcomes (PROs) data is "directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's health, quality of life, or functional status associated with health care or treatment" (Weldring & Smith, 2013, p. 62).

Including PRO data in the care of patients with cancer while receiving treatment is associated with improved quality of life (QOL) and overall survival (Basch et al., 2017; Husson et al., 2020; Wang et al., 2020). There is a ***critical need*** to describe the symptom experience from the patient perspective and develop a reliable measure of the symptom experience specific to patients with melanoma receiving ICI that allows providers to detect symptoms. This data will provide an accurate and reliable diagnosis of symptoms in routine clinical care to inform shared decision-making in treatment planning and for future research purposes.

The ***long-term goal*** is to develop interventions for managing immune-mediated symptoms among patients with advanced melanoma receiving ICIs. The purpose of this proposed mixed-methods study is to describe the patient experience while receiving ICIs for advanced melanoma. The secondary goal is to identify the content domain and initial item generation for an instrument in clinical care and research to evaluate multiple aspects of the symptom experience of patients receiving ICIs for advanced melanoma. To our knowledge, this is the first study to capture the experience of this patient population utilizing the modified MDASI. In pursuit of this, we will accomplish the following specific aims:

1. To describe the symptom burden and how it relates to QOL among patients undergoing ICIs for advanced melanoma across the treatment trajectory.

2. To evaluate the concordance between symptoms communicated during a follow-up visit and reported via PRO measure.
3. To explore the patient experience while receiving ICIs for melanoma using a qualitative approach via patient interviews.

Completion of these aims will yield the following *expected outcomes*: (1) distinct descriptions of the experience of symptoms from the patient perspective, (2) insight into patient communication of symptoms and (3) insight into aspects not previously discussed or included in existing PRO instruments will be explored, allowing the future development of an ICI specific PRO measure for patients with melanoma undergoing ICI, and eventually expanding the use into other cancer disease types utilizing ICI therapy.

Significance

The incidence of melanoma continues to rise annually (*Melanoma of the Skin - Cancer Stat Facts*, n.d.). The 5-year survival of stage I and II melanoma is 98% and 90%, respectively, while stage III ranges from 93% in IIIA to 32% in IIID (Gershenwald et al., 2017). The 5-year survival rate plummets to less than 20% for patients with stage IV disease, where the median survival is between six and seven months (Manola et al., 2000). The treatment landscape has changed drastically from chemotherapy and cytokine-based therapy to immunotherapy and targeted therapy in the past 11 years (Furue & Kadono, 2016). Immunotherapy includes many different agents, but ICIs are the most widely utilized to treat advanced melanoma. ICIs have improved outcomes for those

with advanced melanoma, increasing long-term durable control from 10% up to almost 50% (Carlino et al., 2021; Vaddepally et al., 2020).

ICIs are considered standard of care for managing multiple types of cancer but were first approved by the Food and Drug Administration (FDA) for use in patients with melanoma due to their meaningful clinical benefit to patients (Twomey & Zhang, 2021; Vaddepally et al., 2020). ICIs utilize the innate immune system to elicit anti-tumor activity and eliminate cancer cells by interrupting immune checkpoints anti-CTLA-4, anti-PD-1, and anti-PD-L1; blocking inhibitory interactions between T-cells and other cells and tissues, allowing for unchecked T-cell activation (Furue & Kadono, 2016; Jeurling & Cappelli, 2020; Topalian et al., 2015). The current FDA-approved ICI to treat melanoma are ipilimumab, nivolumab, pembrolizumab, relatilimab + nivolumab, and atezolizumab only with vemurafenib and cobimetinib. Despite the clear benefit of ICIs, there is a risk of irAEs, which occur in up to 90% of patients, and can be permanent and life-threatening if not diagnosed and managed (Brahmer et al., 2018; Schneider et al., 2021, Thompson et al., 2020). The assessment, quantification, and management of irAEs are based on the patient's description of symptoms, diagnostic laboratory results, or imaging results where appropriate, and management of the symptoms while still promoting the anti-tumor impact of the ICI therapy (Abdel-Wahab et al., 2016; Hodi et al., 2010; Thompson et al., 2020).

The patient report of frequency and severity of symptoms from cancer and toxicities from treatment have a poor to moderate association with symptoms and toxicities measured by clinicians (Atkinson et al., 2016; Basch et al., 2009;

Laugsand et al., 2010). Not all patients experience toxicities the same, and the burgeoning area of research around PROs has illuminated the disconnect between what patients experience and what clinicians know (Blood et al., 2021; Mooney et al., 2017; Tolstrup et al., 2019). Symptom assessment and concurrent clinical evaluation to determine if symptom(s) are disease-related or a treatment toxicity, along with subsequent, adequate management are fundamentals of oncology care (American Society of Clinical Oncology & European Society for Medical Oncology, 2006; Cleeland, 2000). The range in severity of grade, onset, and duration of these events are reported with high variability, making it difficult to provide an anticipated pattern of expected irAEs during therapy (Chan & Bass, 2020). The initial clinical trials showed ICI therapy could be toxic with rates of any grade toxicity of up to 99%. The experience of any-grade toxicities ranges from 66% up to 92%, but the rate of Grade 3 or 4 toxicities is 20-55% (Bottomley et al., 2021; Dalle et al., 2021; Kennedy & Salama, 2019; Larkin et al., 2015; O'Reilly et al., 2019; Patrinely et al., 2020; Rogiers, Ley, Lauwyck, et al., 2020). The most frequently experienced irAEs are fatigue, rash, endocrine dysfunction, and diarrhea. All irAEs can potentially be managed with immunosuppressive agents, but can be lethal if not recognized and intervened upon in a timely manner (Furue et al., 2018; Postow, 2022).

Physical toxicities

Pneumonitis, hepatitis, and colitis are frequently discussed in the literature as irAEs, but nearly any organ can be impacted by ICI therapy (Champiat et al., 2016; Chan & Bass, 2020). Certain toxicities are rare but if they occur, they can

impact all aspects of a that patient's life, including Guillian-Barre syndrome, myasthenia gravis, type 1 diabetes, myocarditis, encephalopathy, and severe skin reactions as Stevens-Johnson syndrome (Champiat et al., 2016). The early data published from clinical trials that led to the FDA approval of the ICIs used to treat melanoma did not document these findings; they were discovered and diagnosed in patients utilizing ICI after FDA approval (Hodi et al., 2010a; Larkin et al., 2015; Ribas et al., 2015; Robert et al., 2015; Weber et al., 2015).

Immune-mediated arthritis is a specific toxicity related to ICIs that has been reported in clinical trial data and subsequent retrospective studies, but the timing of onset after ICI initiation remains unclear (Brahmer et al., 2018; Thompson et al., 2020). Immune-mediated arthritis includes inflammatory osteoarthritis, rheumatoid arthritis, polymyalgia rheumatica, synovitis, arthralgias, and myalgias (Belkhir et al., 2017; Cappelli et al., 2018; Lobo et al., 2020). The reported incidence rate of arthritis/arthralgia in previous clinical trials (n=24) ranged from 1%-43% (Cappelli et al., 2017). The limiting factors of clinical trials are: the spectrum of joint pain may not have been captured, cancer types aside from melanoma were included, and clinical trial populations do not represent the "real-world" patient population (Cappelli et al., 2017). Case reports of singular, rare instances of immune-mediated remitting seronegative symmetrical synovitis with pitting edema and Axial Polyarthritis (Feist et al., 2019; Gauci et al., 2017; Ngo et al., 2018) demonstrate that ICI therapy can provoke various toxicities, some still possibly unknown. Without a validated instrument to assess the patient's experience, other toxicities could be under-reported or undetected.

Fatigue was the most common toxicity reported in the initial clinical trials, documented in the early trials at an incidence of 20% up to 39% (Eggermont et al., 2015; Hodi et al., 2010b; Ribas et al., 2015; Robert et al., 2015; J. S. Weber Dr et al., 2015). In the following studies utilizing the health-related quality of life (HRQOL) data captured during these trials, the outcome was that despite toxicities, HRQOL global scores were not impacted (Larkin et al., 2018; Long et al., 2016; Revicki et al., 2012; Schadendorf et al., 2016, 2017; J. Weber et al., 2017). Coens et al. (2017) was the only study to note an impact of fatigue on HRQOL in the patients treated with ipilimumab versus placebo in the adjuvant setting. Further studies in patients outside clinical trials reported fatigue was more intense for patients undergoing treatment with ICI (Lai-Kwon et al., 2019). Fatigue was consistently pointed out as the most frequent long-term toxicity, the cause of the most frequent problems, and impacted physical and social functioning (Lacey et al., 2019; Lai-Kwon et al., 2019; Mamoor et al., 2020).

Emotional toxicities

Participants in each randomized control trial that led to the FDA approval of ipilimumab, pembrolizumab, and nivolumab had a concurrent assessment of HRQOL. The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was utilized in each of the eight studies to assess HRQOL (Coens et al., 2017; Larkin et al., 2018; Long et al., 2016; Petrella et al., 2017; Revicki et al., 2012; Schadendorf et al., 2016, 2017; J. Weber et al., 2017). In addition, five of the eight studies also used the EuroQol (EQ-5D) to assess HRQOL (Larkin et al., 2018; Long et al., 2016; Petrella et al.,

2017; Schadendorf et al., 2017; J. Weber et al., 2017). Both instruments have items that assess emotional impact or toxicity, but it was not documented in any of the eight studies that immunotherapy impacted this. Conversely, literature from patients not participating in clinical trials showed anxiety and depression impacting HRQOL (Lai-Kwon et al., 2019; Milne et al., 2020; Rogiers, Leys, DeCremer et al., 2020; Rogiers, Leys, Lauwyck et al., 2020). These studies' limitations are that they were small, and not all had baseline assessments of anxiety or depression before ICI therapy. Hence, a direct correlation is not feasible but warrants further research.

The purpose of QOL instruments is to describe the impact of disease on the status of function, activity, and participation; these components are considered most relevant to patients and society regarding health status (Cieza & Stucki, 2005). QOL is also noted to be "a broad-ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment" (Power et al., 1998, p. 1570). The measure of QOL is a person's perception and goals; it tends to be unstable and does not always match the status of the other health concepts presented in the conceptual model of patient outcomes (Wilson & Cleary, 1995). Assessing symptoms and how they impact QOL allows the patient to describe which symptoms are occurring and how they affect their perceived QOL, which is essential to clinicians for creating a management plan. Supplementing survey-collected PRO data with cognitive

interviews will allow providers and researchers to gain more clinically meaningful data regarding specific items impacting their HRQOL (Holch et al., 2016).

It appears ICIs are generally well tolerated in that despite symptoms, and patients rate their Global HRQOL Score as high and similar to baseline before ICI therapy (Abdel-Rahman et al., 2018; Boutros et al., 2021; Hall et al., 2019; Kent et al., 2015; Malkhasyan et al., 2017). Global HRQOL scores were lower in patients who reported poor physical health or poor psychological health, and even lower when both were present (Cornish et al., 2009). Utilizing the EORTC-QLQ-C30, global HRQOL scores at baseline were similar between the ICI arm and chemotherapy arm, but then global scores at 12 weeks and later had improved in patients undergoing therapy with ICI, while scores declined in patients undergoing chemotherapy (Long et al., 2016; Schadendorf et al., 2016). Comparing ICI versus placebo or ipilimumab versus nivolumab, symptom burden was higher in the ICI or ipilimumab arm. Still, QOL scores did not decrease to the point of clinical significance. The data lacking from the previous studies is the individual functioning scores, such as cognitive and emotional functioning, or if there is any detectable difference by assessment of symptoms and HRQOL with a melanoma-specific instrument. There was no discussion of the data about mental health (i.e., anxiety or depression) despite patients diagnosed with metastatic melanoma being at higher risk for anxiety or depression (Beutel et al., 2015; Vojvodic et al., 2018). Depression was considerably higher in melanoma survivors than in the general population, and anxiety was higher in female survivors with increased symptom reporting and decreased physical functioning

(Beutel et al., 2015; Boekhout et al., 2021; Mamoor et al., 2020; Rogiers et al., 2020). Expanding PRO measures into the community clinical practice is essential to ascertain patient experiences while undergoing ICI therapy.

PRO data is "directly reported by the patient without interpretation of the patient's response by a clinician or anyone else and pertains to the patient's health, quality of life, or functional status associated with health care or treatment" (Weldring & Smith, 2013, p. 62). PRO data improves communication between patients and providers and can augment clinician safety evaluation of treatments with each treatment cycle, providing descriptive data on the timing, duration, and severity of adverse events (Basch et al., 2009; King-Kallimanis et al., 2019). ICI toxicities are unique in that they can appear at various timepoints, wax and wane in severity, and become permanent and potentially lethal (Furue et al., 2018; Kennedy & Salama, 2020). Expanding PRO measurement into community clinical practice is vital to ascertain the patient experience while undergoing ICI therapy for advanced melanoma in both the adjuvant and metastatic settings. Obtaining PRO data during the care of patients with cancer while receiving treatment is associated with improved QOL and overall survival (Basch et al., 2017; Husson et al., 2020). The National Institutes of Health have created a bank of validated, evidenced-based questions to assess the standard areas of QOL-pain, fatigue, physical and social functioning, and emotional distress (Cella et al., 2007). The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) endorse the inclusion of PRO outcomes and QOL

assessment within clinical trials and community care of oncology patients (Cherny et al., 2015; Schnipper et al., 2016).

There are a variety of PRO measures available to assess symptoms and HRQOL in patients with cancer, and doing so at regular intervals can improve communication and outcomes (Graupner et al., 2021; Kotronoulas et al., 2014; Velikova et al., 2004). The most significant concern with the current PRO instruments is all were created and validated prior to ICI therapy availability. The MD Anderson Symptom Inventory (MDASI) is a multi-symptoms PRO Measure used in both clinical and research applications (Cleeland, 2000). The MDASI core has evidence of validity in the oncology population (n=527) with the principal axis factor analysis that revealed two underlying constructs: (1) general symptom severity and (2) a gastrointestinal factor. Evidence of reliability for "the two sets of symptom items and the interference scales, respectively, were α of 0.85, 0.82, and 0.91 for the validation sample and α of 0.87,0.87, and 0.94 for the cross-validation sample" (Cleeland, 2000, p. 1642). This instrument has evidence of reliability and validity in multiple cancer populations, with 19 separate modules for specific treatment or cancer diagnosis but has not been evaluated in patients with advanced melanoma or patients undergoing ICI therapy (Armstrong et al., 2006; Gning et al., 2009; Mendoza et al., 2011; Wang et al., 2010). In addition, the MDASI system include and item library comprehensive of symptoms that have been cognitively debriefed and validated with patients experiencing these symptoms. The expert faculty at MD Anderson will tailor a modified MDASI questionnaire to meet the needs of the study.

The Functional Assessment of Cancer Therapy- Melanoma (FACT-M); (Cormier et al., 2008) is the only validated melanoma-specific instrument to assess symptoms and impact on HRQOL. It focused on the post-surgical time point and was created before ICI development. Cormier et al. (2008) found the internal consistency and test-retest reliability (r) of the melanoma subscale (Cronbach α = .85, r = .81) and the total FACT-melanoma (α = .95, r = .90). The Functional Assessment of Cancer Therapy- General (FACT-G); (Cella et al., 1993) was developed to assess HRQOL and has evidence of validity and reliability in patients with cancer (Brucker et al., 2005; Victorson et al., 2008). The clinical trials, each with hundreds of participants that led to the FDA approval of the current ICIs utilized the EORTC QLQ-C30 (Aaronson et al., 1993) and the EQ-5D (Rabin & de Charro, 2001) almost exclusively (Larkin et al., 2018; Long et al., 2016; Petrella et al., 2017; Revicki et al., 2012; Schadendorf et al., 2016, 2017; Weber et al., 2017). Though EQ-5D has been validated in patients with cancer, there is not a specific study of patients with melanoma. The EORTC QLQ-C30 has been validated in the oncology population (Groenvold et al., 1997) but not specifically in patients with melanoma undergoing ICI. A melanoma-specific version, the EORTC QLQ-Melanoma 38, is undergoing current research to see if reducing it to 28 questions is better (Winstanley et al., 2020). Fatigue is the symptom most often reported by patients with cancer (Glaus et al., 1996). An unpublished systematic review by the PI found that fatigue was the most common toxicity reported while undergoing ICI treatment but had a diverse impact on QOL. The lack of data in this specific population of patients with

melanoma undergoing ICI therapy exposes the need for research with disease and treatment specific instruments to capture the accurate patient experience.

The ongoing COVID-19 pandemic has altered how cancer care is delivered, as there has been an increase in telehealth utilization for treatment clearance visits to minimize patient exposure when possible (CDC, 2020). Telehealth involves visits via video applications, patient portals, or phone calls. Telehealth has increased access to care for some patients with less travel or time in waiting rooms and remains preferred to in-person visits when feasible (Schrag et al., 2020). Given this shift in clinical care, methods for systematically measuring PROs in the outpatient setting and remote care are needed. Evidence supports that PRO data collected electronically can be comparable to paper-based data collection, particularly with screen-based devices (Byrom et al., 2019; Gwaltney et al., 2008). Electronic capture of PRO data also minimizes transcription errors, improves compliance, and minimizes missing data (Coons et al., 2015). Importantly, for remote and electronic capture of PRO data to be useful, valid and reliable measures are needed that address the unique needs of specific patient populations, such as those with melanoma while undergoing ICI therapy.

The theory underpinning this proposal is the "conceptual model of patient outcomes" (Wilson & Cleary, 1995), consisting of five levels of health concepts, each building on the previous and in complexity. The five levels are (1) biological and physiological factors, (2) symptoms, (3) functioning, (4) general health perceptions, and (5) overall quality of life. This model was chosen as the

conceptual framework for this proposal because it provides a pathway for PRO data to be understood and applied in clinical care to personalize and improve patient care. Symptoms can be physical, psychophysical (i.e., those not distinctly physical or psychological), and emotional and psychological symptoms (e.g., fear). Symptoms are not always directly related to the severity of biological factors. Some conditions (e.g., depression or pain) do not have an objective measure but rely on patient-report of symptoms (Wilson & Cleary, 1995). Due to the dynamic nature of melanoma and symptoms, it is paramount to involve the patient in every aspect of their care, especially when there is a current lack of disease- and treatment-specific instruments to assess their experience.

Innovation

This study is a proposed mixed-methods study to evaluate the symptom experience of patients receiving ICI for treatment of melanoma. This proposed study is innovative in several ways: (1) This cross-sectional, mixed-methods approach is an innovative way to evaluate ICI-induced symptoms. This study is the first in patients with melanoma across different time points of ICI therapy dosing to evaluate symptoms with the modified MDASI. (2) Though previous studies have utilized both quantitative PRO data and semi-structured interviews to discover the patient perspective of ICI therapy and its impact on QOL (Rogiers, Leys, De Cremer, et al., 2020; Rogiers, Leys, Lauwyck, et al., 2020), this study will obtain the patient perspective about the integrity of current instruments utilized to assess their symptom experience. (3) Additionally, we will complete qualitative interviews with a cohort of patients who are not reporting

any symptoms in the clinic. The goal is to determine if an open-ended question about their experience reveals that they are experiencing a symptom that is not captured clinically using the current instruments or clinical evaluation. These interviews may also expose characteristics of patients that are not experiencing symptoms and provide insight into potential protective mechanisms.

Preliminary Studies

The PI has completed but not yet published two previous literature reviews regarding the toxicities of ICI therapy. The earlier review evaluated the current knowledge, description, and management of immune-mediated arthritis. Discovering that this toxicity is not singularly defined and, despite guidelines, is still difficult to diagnose, delaying management and impacting patient outcomes. The most recent review evaluated current knowledge about the impact of ICI therapy on HRQOL. With current instruments, most patients noted that even with toxicities of any severity, there was no decline in HRQOL. A small portion of studies utilized multiple instruments to evaluate the patient and toxicities and noted a negative impact on HRQOL. The outcome of these studies further supported the need for the research proposed here, evaluating symptom burden while undergoing ICI, impact on HRQOL, and a qualitative interview to ascertain the validity and accuracy of the data captured with the included instruments.

Approach

Specific Aim #1 To describe the symptom burden and how it relates to QOL for patients undergoing ICIs for their advanced melanoma across the treatment trajectory.

Design and Setting

This study will be a cross-sectional mixed-methods study to evaluate the patient experience of symptoms while undergoing ICIs to treat advanced melanoma. To answer Aim 1, we will evaluate the symptom experience using a modified MDASI (Cleeland, 2000) with items from the MDASI symptom library and HRQOL using the FACT-M (Cormier et al., 2008). We will include patients currently receiving ICI treatment at MD Anderson Cancer Center (MDACC) who are being evaluated virtually or in person at the Medical Melanoma clinic. The clinic is located in the Main Building at 1515 Holcombe Blvd., Houston, TX, and is labeled the Melanoma and Skin Center.

Population and Sample

We will recruit 60 patients who meet the inclusion criteria. While not obtained with a power calculation, 60 participants allows for adequate description of the experience for this pilot work. This number was not obtained with a power calculation as this is a descriptive study utilizing the modified MDASI and FACT-M in patients with melanoma. As seen in Table 1, sampling will be purposive based on key characteristics of the patients (e.g., gender, age, ethnicity, time on therapy, etc.) to ensure the diversity of the melanoma population undergoing ICI

treatment is sampled. There are over 100 patient appointments per week in the Melanoma Clinic at MDACC. At least 25 patients each week are presently on immunotherapy, and at least 5 of these patients, anecdotally, have at least one toxicity symptom. This study aims to recruit patients with and without symptoms to ensure we are not missing an aspect of the symptom experience not captured by the current standard-of-care symptom evaluation. The PI is confident in recruiting the needed sample to address the aims due to the frequency of visits and the number of patients meeting the eligibility criteria.

Inclusion criteria include 1) diagnosis of melanoma, 2) actively receiving treatment with ICI; 3) ability to read and speak English; 4) has a device with Internet access that could be utilized for receiving the link to RedCap or for secure videoconferencing to complete the surveys; 5) has the ability to travel to the coordinating center if they do not wish to do the surveys remotely, and 6) are willing and able to provide written informed consent before enrollment.

Exclusion criteria include 1) on ICI therapy that is in combination with any drug except another ICI 2) serious medical illness (e.g., uncontrolled hypertension, heart failure, history of acute myocardial infarction); 3) alcohol/substance abuse or cognitive impairment, 4) pregnancy or lactation; 5) evidence of cognitive impairment as documented in the medical record, and 6) hospitalization within the preceding year for psychiatric illness.

Procedure for Data Collection

The PI and current research staff in the Melanoma Research department will screen each clinic day for patients with a pending or active treatment plan, including ICIs. There is a note that can be sent electronically to inform the patient of their eligibility and to see if they would like to participate. After providing informed consent, the one-time surveys of the FACT-M (Cormier et al., 2008) and the modified version of MDASI core will be considered evaluable if completed within 72 hours of the clinic visit. If this is not completed by 24 hours a reminder phone call, email or in-basket message will be sent to the patient. Another reminder will be sent at 48 hours. If still not completed the patient would be removed from the study as this data is essential. Study data will be collected and managed using REDCap electronic data capture tools hosted at UT Cizik School of Nursing (Harris et al., 2009, 2019). "REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources" (*Citations – REDCap*, n.d.). Based on patient preference, we will provide either an iPad to use in the clinic, a link to Redcap sent to a preferred email, or a message via the electronic health record MyChart in EPIC. The links allow the patient to complete the surveys when convenient, within 48 hours of the clinic visit, and will enable us to include patients who cannot travel to

Houston for therapy. Sociodemographic data will be collected from the participant and from the medical record, including age, gender, race, marital status, years of education, employment status, co-morbidities (measured with Charleston Comorbidity Index, type of ICI, current medications, and American Joint Committee on Cancer (AJCC) Stage of melanoma (Behbahani et al., 2020; Ikeguchi et al., 2020).

Instruments

The MDASI core (Appendix A) a is a self-report multi-symptom PRO measure for clinical and research use (Cleeland, 2000). The MDASI has evidence of validity in the oncology population (n=527) with the principal axis factor analysis that revealed two underlying constructs: (1) general symptom severity and (2) a gastrointestinal factor. A cross-sample validation was completed with 113 participants that further supported the validity with a standard deviation of the residual of 0.05, and the standard error of the correlation coefficient was 0.09. Evidence of reliability for "the two sets of symptom items and the interference scales, respectively, were α of 0.85, 0.82, and 0.91 for the validation sample and α of 0.87,0.87, and 0.94 for the cross-validation sample" (Cleeland, 2000, p. 1642). The MDASI has been modified to be used in 19 other specific cancers and treatments. There is a MDASI symptom library (Appendix B) is available to be added to the MDASI core to create an experimental MDASI that is tailored to this clinical research, patients with melanoma undergoing ICI Therapy. The items are added to the end of the MDASI core to maintain the integrity of its psychometric validity. The items included for the modified MDASI

in this study were selected by consensus of four melanoma clinical experts. An item was included if 2 or more experts agreed it should be included. As required, the items will be added to the end of the MDASI-core and this is the final instrument that will be utilized in this study. This instrument is assessing symptoms in the past 24 hours and should take about 5-10 minutes to complete.

The FACT-M (Appendix C) is a self-report 51-item questionnaire designed to measure five domains of HRQOL in patients with melanoma: physical, social, emotional, functional well-being and a Melanoma subscale. Cormier et al. (2008) completed a process with multiple tests, completed by 273 patients, aged 18 or older, with melanoma of all stages (I-IV), to evaluate evidence of validity, reliability, and sensitivity in patients with cancer. Cormier et al. (2008) found the internal consistency and test-retest reliability (r) of the melanoma subscale (Cronbach α = .85, r = .81) and the total FACT-melanoma (α = .95, r = .90) which are evidence of the reliability and validity of the instrument (Carmines & Zeller, 1979). The FACT-M can be self-administered or done by interview, assess symptoms over the past 7 days and takes about 10-15 minutes to complete.

Specific Aim #2 To evaluate the concordance between symptoms communicated during a follow-up visit and reported via PRO measure.

Design and Setting

The patient will undergo their standard clinic evaluation as part of routine care, including a review of systems (ROS) completed by the clinical team and documented in the electronic clinical record per clinic flow. To prevent bias the PI

will not be the clinician of the participant at the visit where they are completing the surveys so the ROS will be extracted from the electronic health record, including the nurse ROS, the advanced practice provider ROS, and if applicable the physician ROS.

Sample

We will include data for all 60 study participants in the Aim 2 analysis.

Procedure for Data Collection

ROS data from the follow-up visit immediately preceding PROs completion will be extracted from the medical record by the PI and documented in REDCap. The PI will compare symptoms reported in the ROS and symptoms reported via PRO instruments (modified MDASI and FACT-M) per patient. The results will be documented as a 1= complete match of symptoms reported in ROS and in instrument, a 2 = not a match but less than 3 items reported on ROS but were not reported in instrument, 3 = not a match, 3 or more symptoms reported in ROS but were not reported in instruments, 4 = not a match, but less than 3 symptoms reported in instruments than were not reported in ROS or a 5= not a match, 3 or more symptoms reported in instruments than were not reported in ROS. Please see Table 2 for an example of how it will be documented.

Specific Aim #3 To explore the patient experience while receiving ICIs for melanoma using a qualitative approach via patient interviews.

Design and Setting

We will conduct a phenomenological qualitative study to evaluate the patient's symptom experience while undergoing ICI treatment for melanoma. The patients will describe their experience and explore whether any aspects of the experience are not captured with current assessment instruments.

Sample

The PI will contact a subset of study participants (approximately 20 patients) who completed the modified MDASI and FACT-M surveys. Sampling for interviews will be purposive (see Table 3) based on key characteristics of the patients (gender, age, race, ethnicity, symptom status, etc.) to ensure the breadth of the ICI experience is captured.

Procedure for Data Collection

To capture the relevant patient experience and minimize recall bias, approximately 20 patients will participate in a semi-structured qualitative interview within two weeks of completing the PRO surveys. The interview will be conducted via phone, teleconference, or in-person, with the final sample size determined by saturation, a method of determining sample size to obtain the maximum amount of information possible (Parse et al., 1985). Sampling will be purposive based on key characteristics of the patients (gender, age, race, ethnicity, etc.) to ensure the breadth of the symptom experience is sampled. After providing informed consent, informants will participate in a single digitally recorded interview lasting approximately 30 minutes. The recording will be

transcribed verbatim by a professional transcriptionist, and accuracy verified by the interviewer.

Qualitative research interviews are used to examine the reality of individuals and their perceptions and gain more understanding of events (Bolderston, 2014). To assess the patient experience, qualitative interviews will be completed using an interview guide containing open-ended questions with each participant and conducted by the Principal Investigator, Natalie Jackson (NJ), who has experience in qualitative interviewing (Creswell & Poth, 2018; Polit & Beck, 2021).

Instruments

To ensure the credibility of the interview guide, the questions were developed in conjunction with clinical experts in the care of patients with melanoma receiving ICI (Kallio et al., 2016). During the analysis phase the PI will take the qualitative findings and reach out to at least 5 of the 20 participants to validate the findings interpreted from the interviews accurately represents their views and experience.

The Qualitative interview guide is seen in Figure 1.

Analysis

Descriptive statistics will be used to describe the participant sample based on demographic and clinical characteristics. The Principal Investigator (NJ) will take the survey data captured in Redcap and, with the assistance of a statistician

and the software SPSS (*IBM SPSS Statistics*, 2020), test reliability by assessing Cronbach's alpha of the modified MDASI and FACT-M in this study (Specific Aim 1). An α greater than .80 is considered adequate evidence of reliability when using an established instrument (Carmines & Zeller, 1979). The independent variable is the time on treatment categorized by separate 12-week blocks. If the data has a normal distribution, a one-way ANOVA will be completed with the continuous variable, and Chi-Square will be completed for the categorical variables. If the data does not have a normal distribution, the Kruskal-Wallis test will be conducted. For Specific Aim 2, the PI will document the frequency of ROS matching or not matching the PROs report. The proportion of symptom reports completed by patients vs clinicians will be tabulated to compare the extent of missing data between these two reporting approaches. Descriptive statistics will be used to describe the participant sample based on demographic and clinical characteristics.

The Principal Investigator (NJ) will analyze the interview transcripts using MAXQDA qualitative software (VERBI Software, 2021); (Specific Aim 2), with an adaptation of descriptive exploratory analysis (Parse et al., 1985). Another researcher experienced in qualitative methods, Meagan Whisenant (MW), will independently examine the interview transcripts and identify themes for cross-validation. The Principal Investigator will compile a list of all aspects of the experience mentioned by patients in the interviews. The research team will then review the list and reduce the number of noted experiences by removing those that are overlapping. If agreement cannot be reached about an experience, it will

be left on the list. The PI will also discuss the findings with participants to further validate the data (Polit & Beck, 2021).

The qualitative data from the interviews will contribute to the validity of the accepted measurement instruments or provide evidence of a gap in the assessment that requires modifications to current instruments or the creation of a new instrument.

Potential Limitations, Alternative Strategies, and Future Extensions

As with any cross-sectional study, especially in the vulnerable population of people with cancer, there are potential problems with timely accrual, missing data, and retention. The team has experience overcoming these potential hurdles by tracking accrual and adjusting procedures as needed via a weekly audit that the PI will conduct to assess recruitment, enrollment, adherence, complete data collection, and retention. The PI will set calendar reminders to ensure the interview has been transcribed, verified, and reviewed within three weeks of availability to allow for adjustment of interview questions to increase the breadth and validity of data collected about the patient's experience of joint pain while on ICI.

Human Subjects Research

Protection of Human Subjects

Participation in this study is entirely voluntary. The known risk with all research, including protected health information, there is the risk of a data

breach. The investigators will maintain strict patient confidentiality. Cases will be coded by de-identified study number. All data will be stored in the secure UTHealth REDCap server.

Data Safety Monitoring Plan: If a participant rates their physical or emotional symptom distress at a severe level (7 or higher), an email will be generated automatically and sent to the study staff. The study staff will notify the clinician team caring for the patient to make appropriate referrals. If a patient reports a severe symptom or suicidal ideation during data collection, we will inform the social workers in melanoma and escort them to the Acute Cancer Care Center (ACCC) at MDACC per hospital guidelines. The informed consent notifying patients of the approximate time commitment to complete the surveys and that there is no anticipated immediate benefit to their care. For the patients proceeding with the voluntary interview, there is an additional informed consent noting the approximate time commitment and that there is no anticipated immediate benefit to their care. The characteristics of the study participants are described in Tables 1 and 3.

Timeline

The first quarter of Year 1, which starts May 2022, will be devoted to the study initiation procedures, including institutional review board approvals, staff training, and refining the interview guide. The PI will submit for approval from the institutional review boards at MDACC and UT CSON before the anticipated study start. Enrollment will begin in the second quarter of Year 1 and continue through

the end of the fourth quarter of Year 1. The PI will complete data analysis in the first quarter of Year 2 and develop abstracts and manuscripts in the second quarter of Year 2. Please see Table 4 for further details.

Biosketch

proposed study is a multidisciplinary effort among the members of the Research Team, who each bring their own field of expertise to the effort. Ms. Natalie Jackson, Ph.D. (c), APRN (The University of Texas MD Anderson Cancer Center (MDACC)), will serve as the study's Principal Investigator. Ms. Jackson is an expert in caring for patients with melanoma and has experience managing melanoma and ICI therapy. Ms. Jackson has experience conducting qualitative interviews with cancer patients and caregivers. The Chair of the Dissertation Committee, Dr. Meagan Whisenant Ph.D., APRN (The University of Texas Health Science Center at Houston Cizik School of Nursing (UT CSON) and MDACC) who is an expert in studying patient-reported outcomes, development, and validation of PRO measures, and utilizing qualitative approaches for understanding the patient experience. Dr. Constance Johnson, Ph.D., MS, RN, FAAN, is the Associate Dean for research at UT CSON and the first recipient of the Maria C. and Christopher J. Pappas Family Distinguished Chair in Nursing. She is an expert in primary research and informatics with a focus on health promotion and disease prevention. Dr. Hussein Tawbi MD, Ph.D. (MDACC) is a Professor, the Deputy Chair, and Director of Personalized Cancer Therapy in the Department of Melanoma Medical Oncology. He continues to be active in research as a PI on multiple clinical trials and most recently published data that

led to the FDA approval of new therapy for advanced melanoma, Opdualag®. Dr. Shelley Wang, MD Ph.D. (MDACC), is a Professor of symptom research. Each member brings their research experience to provide expertise in ICI therapy, qualitative approaches, development and use of PRO instruments, and qualitative and quantitative data analysis.

Future directions after this study are to define the content domain and initial item generation and specification for a PRO measure of toxicities among patients with melanoma receiving ICIs if current instruments prove to be inadequate. If there is evidence of a disconnect between patient reported symptoms in clinic compared to an instrument survey, this will provide another avenue for more exploratory research. If the instruments prove adequate, further research to assess the feasibility, acceptability, and eventually benefit of non-pharmacological interventions to manage symptoms of ICI therapy in patients with advanced melanoma and other cancers.

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Table 1

The Minimum Proposed Subject Characteristic percentages for Quantitative Assessment of the Symptom Experience in Metastatic Melanoma Patients on ICI (N=60)

Age		Gender		Stage		Race/Ethnicity				Symptoms on ROS		Time on ICI therapy (months)			
< 65	≥ 65	Male	Female	Stage III	Stage IV	White	Asian	Black	Hispanic	Yes	None	1 -3	3-6	6 -9	9 – 12
35 %	50 %	40 %	40 %	30 %	30 %	35 %	5 %	5 %	5 %	50 %	20 %	20 %	20 %	20 %	20 %
21	30	24	24	18	18	21	3	3	3	30	12	12	12	12	12

Note. (*) totals will not equal (n =60) as this is to represent the minimum enrollment of each characteristic

Table 2

Capturing the Degree of Matching between ROS and PRO

Clinician ROS	MDASI	FACT-M			
Nurse					
APP					
MD					

Note. 1= complete match of symptoms reported in ROS and in instrument, a 2 = not a match but less than 3 items reported on ROS but were not reported in instrument, 3 = not a match, 3 or more symptoms reported in ROS but were not reported in instruments, 4 = not a match, but less than 3 symptoms reported in instruments than were not reported in ROS or a 5= not a match, 3 or more symptoms reported in instruments than were not reported in ROS.

Table 3

The Proposed Subject Characteristic percentages for Qualitative Assessment of the Symptom Experience in Metastatic Melanoma Patients on ICI (N=20)

Age		**Gender**		**Stage**		**Race/Ethnicity**				**Symptoms on ROS**		**Time on ICI therapy (m=months)**			
< 65	**> 65 =I**	**Male**	**Female**	**Stage III**	**Stage IV**	**White**	**Asian**	**Black**	**Hispanic**	**Yes**	**None**	**1 m– 3 m**	**3 m – 6 m**	**6 m – 9 m**	**9 m – 12 m**
40 %	40 %	40 %	40 %	35 %	30 %	35 %	5 %	5 %	5 %	50 %	20 %	20 %	20 %	20 %	20 %
8	8	8	8	8	7	7	1	1	1	10	4	4	4	4	4

Note. (*) totals will not equal (n =20) as this is to represent the minimum enrollment of each characteristic

Table 4

Timeline of Study Activities

Activity	Year 1 (May 22- April 23)				Year 2 (April-Aug 23	
Quarter (Q)	Q1	Q2	Q3	Q4	Q1	Q2
Study startup						
Enrollment/Instrument completion		10	20	30		
Qualitative Interview & transcriptions		3	6	7	4	
Data analysis						
Dissemination/Graduation						

Figure 1

Interview Guide

1. What is it like for you to undergo treatment with ICI [specific name] for your advanced melanoma?
2. Potential additional probe questions if patient does not describe spontaneously
    a. What symptoms are you experiencing?
    b. How is (ask with name of each individual symptom mentioned by patient, one symptom at a time) impacting your daily activities?
        - Have all the important aspects of your ICI experience been described?
        - What was it like for you when you first had melanoma and started ICI?
3. Potential additional probe questions if patient does not describe spontaneously
    a. What symptoms were you experiencing? If you are having trouble eliciting symptoms, ask the patient, "What symptoms did you notify the doctor about while undergoing ICI therapy?"
    b. How did ICI therapy impact your daily activities?
        - What other symptoms have you experienced that were related to melanoma or ICI therapy?
4. Potential additional probe questions if patient does not describe spontaneously
    a. What symptoms did you experience when you were having treatment with ICI?
    b. What treatment or procedure were you receiving when these symptoms occurred?
    c. How did (ask with name of each individual symptom mentioned by patient, one symptom at a time) impact your daily activities?
        - Have all the important aspects of experiencing therapy with ICI been described?
        - What do you see happening in the future with your melanoma?
5. Are there any other aspects of experiencing treatment with ICI that you would like to tell me about?
6. Is there anything else important about having advanced melanoma that you would like to tell me

Note. Questions asked for the semi-guided interviews

Appendix A

Sample of the MDASI

Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

MD Anderson Symptom Inventory (MDASI) Core Items

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

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Date: _____ Institution: _____

Participant Initials: _____ Hospital Chart #: _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. [illegible] your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
14. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
15. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
16. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
17. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
18. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
19. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

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Appendix B

The MDASI Symptom Library

	SYMPTOM		SYSTEM
1	Your problem with ankle swelling at its WORST?		Cardio/Circulatory
2	Your problem with racing heartbeat or palpitation at its WORST?		Cardio/Circulatory
3	Your chest heaviness or tightness at its WORST?		Cardio/Circulatory
4	Your problem with paying attention (concentrating) at its WORST?		Cognitive
5	Your problem with remembering things at its WORST?	Core	Cognitive
6	Your difficulty speaking (finding the words) at its WORST?		Cognitive
7	Your itching at its WORST?		Cutaneous
8	Your rash at its WORST?		Cutaneous
9	Your skin problems at its WORST?		Cutaneous
10	Your problem with feeling cold at its WORST?		Endocrine
11	Your problem with feeling hot at its WORST?		Endocrine
12	Your night sweats at its WORST?		Endocrine
13	Your problem with sweating at its WORST?		Endocrine
14	Your hot flashes at its WORST?		Endocrine
15	Your problem with lack of energy at its WORST?		General
16	Your fatigue (tiredness) at its WORST?	Core	General
17	Your constipation at its WORST?		Gastrointestinal
18	Your diarrhea at its WORST?		Gastrointestinal
19	Your diarrhea, or watery stools via stoma (abdominal opening) at its WORST?		Gastrointestinal
20	Your feeling bloated at its WORST?		Gastrointestinal
21	Your pain in the abdomen at its WORST?		Gastrointestinal
22	Your inability to eat at its WORST?		Gastrointestinal
23	Your regurgitation (acid reflux) at its WORST?		Gastrointestinal
24	Your nausea at its WORST?	Core	Gastrointestinal
25	Your problem with lack of appetite at its WORST?	Core	Gastrointestinal
26	Your vomiting at its WORST?	Core	Gastrointestinal
27	Your feeling of malaise (not feeling well) at its WORST?		General
28	Your fever or chills at its WORST?		General
29	Your balance or falling at its WORST?		General
30	Your pain or burning with urination at its WORST?		Gynecologic/Urinary
31	Your urinary urgency at its WORST?		Gynecologic/Urinary
32	Your vaginal discharge at its WORST?		Gynecologic/Urinary
33	Your inability/difficulty urinating at its WORST?		Gynecologic/Urinary
34	Your bruising easily or bleeding at its WORST?		Hematologic
35	Your irritability at its WORST?		Mood
36	Your feelings of being distressed (upset) at its WORST?	Core	Mood
37	Your feeling sad at its WORST?	Core	Mood
38	Your joint stiffness or soreness at its WORST?		Musculoskeletal
39	Your muscle soreness or cramping at its WORST?		Musculoskeletal
40	Your muscle weakness at its WORST?		Musculoskeletal
41	Your weakness in the arms and/or legs at its WORST?		Musculoskeletal
42	Your back pain at its WORST?		Musculoskeletal
43	Your bone aches at there WORST?		Musculoskeletal
44	Your dizziness at its WORST?		Neurological
45	Your numbness or tingling at its WORST?	Core	Neurological
46	Your choking at its WORST?		Oral
47	Your difficulty swallowing at its WORST?		Oral
48	Your difficulty chewing at its WORST?		Oral
49	Your hoarseness at its WORST?		Oral
50	Your mouth/throat sores at its WORST?		Oral
51	Your problem with mucus in mouth or throat at its WORST?		Oral
52	Your problem with your teeth or gums at its WORST?		Oral
53	Your sore mouth or throat at its WORST?		Oral
54	Your hoarseness or voice changes at its WORST?		Oral
55	Your having a dry mouth at its WORST?	Core	Oral
56	Your headache at its WORST?		Pain
57	Your pain at its WORST?	Core	Pain
58	Your eye problems at there WORST?		Perceptual
59	Your changes in vision at its WORST?		Perceptual
60	Your coughing at its WORST?		Respiratory
61	Your shortness of breath at its WORST?	Core	Respiratory
62	Your problem with bitter taste at its WORST?		Perceptual
63	Your change in taste at its WORST?		Perceptual
64	Your changes in sexual function at its WORST?		Sexual
65	Your disturbed sleep at its WORST?	Core	General
66	Your feeling drowsy (sleepy) at its WORST?	Core	General
67	Your swelling of your hands, legs, feet, abdomen, or around your eyes at its WORST?		General

Appendix C

Sample of the FACT-M

FACT-M (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
M1	I have pain at my melanoma site or surgical site	0	1	2	3	4
M2	I have noticed new changes in my skin (lumps, bumps, color(colour))	0	1	2	3	4
M3	I worry about the appearance of surgical scars	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
PTA4	I have to limit my physical activity because of my condition	0	1	2	3	4
Aa10	I get headaches	0	1	2	3	4
Hsp3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
M5	I have aches and pains in my bones	0	1	2	3	4
M6	I have noticed blood in my stool	0	1	2	3	4
PTA3	I have to limit my social activity because of my condition	0	1	2	3	4
MS8	I feel overwhelmed by my condition	0	1	2	3	4
M8	I isolate myself from others because of my condition	0	1	2	3	4
M9	I have difficulty thinking clearly (remembering, concentrating)	0	1	2	3	4
HF7	I feel fatigued	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	At the site of my melanoma surgery:	Not at all	A little bit	Some-what	Quite a bit	Very much
M10	I have swelling at my melanoma site	0	1	2	3	4
M11	I have swelling as a result of surgery	0	1	2	3	4
M12	I am bothered by the amount of swelling	0	1	2	3	4
M13	Movement of my swollen area is painful	0	1	2	3	4
M14	Swelling keeps me from doing the things I want to do	0	1	2	3	4
M15	Swelling keeps me from wearing clothes or shoes I want to wear	0	1	2	3	4
M16	I feel numbness at my surgical site	0	1	2	3	4
M17	I have good range of movement in my arm or leg	0	1	2	3	4

"The Symptom Experience of Patients with Advanced Melanoma Undergoing Immune Checkpoint Inhibitor (ICI) Therapy."

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Abstract

Background: The advent of immune checkpoint inhibitor (ICI) therapy has vastly improved outcomes for patients with advanced melanoma. However, the symptom burden and intensity with its impact on quality of life (HRQoL) and functionality is heterogeneous and unpredictable. Patient-reported outcomes (PRO) have improved our knowledge of the patient perspective, but data is still limited.

Objectives: To explore the patient's account and gain a deeper understanding of their lived experience while undergoing ICI therapy for their advanced melanoma.

Methods: A qualitative study design utilizing descriptive exploratory content analysis from interviews as well as quantitative data about their symptom burden and interference with the PRO instruments. The 19 participants with advanced melanoma undergoing ICI therapy completed the Modified MDASI and FACT-M and then recorded semi-structured interviews. Interpretive description informed the inductive and iterative analysis approach.

Results: Participants had a heterogenous experience of ICI and melanoma-related symptoms; distress (84%), fatigue (68 %), rash or skin changes (53%), pain (30%), diarrhea (30%), itching (26%) and shortness of breath (21%). There was a range of interference with HRQoL domains, mood (47%), relations with other people (26%), activity (21 %), as well as those who noted a lack of physical interference (79%). Uncertainty was a pervasive theme in the interviews (68%) despite the majority having positive thoughts on ICI therapy (58%) and expectations of the success of therapy (53%).

Conclusions: The physical and emotional burden of a melanoma diagnosis, undergoing therapy, and the uncertainty of the outcomes are pervasive for patients. Communication surrounding the diagnosis, prognosis, treatment options, and outcomes needs to be clear and acknowledge there are unknowns. Providers may benefit from utilizing a validated PRO instrument to help evaluate and understand the patient's symptom experience while undergoing ICI therapy.

Introduction

Melanoma is the deadliest skin cancer, with an estimated 97,610 new cases of melanoma in 2023 accounting for 5% of all new cancer diagnoses and 7,990 deaths, accounting for 1.3% of all cancer deaths (*Melanoma Skin Cancer Statistics*, n.d.) Though it is estimated only 2.1% of people will be diagnosed with melanoma in their lifetime, when diagnosed, the outcome is uncertain. This is evident as survival rates for Stage IV were not included in the AJCC 8th edition staging due to heterogenous response rates to the advanced therapeutics of targeted therapy and immunotherapy (Keung & Gershenwald, 2018).

In recent years, a relatively novel class of therapeutics, immune checkpoint inhibitors (ICIs), has been approved for use in various cancer diagnoses, depending on disease staging. In patients with advanced melanoma, the Food and Drug Administration recently approved the extended use of pembrolizumab in the adjuvant setting from Stage III into earlier stage melanoma IIB and IIC (Luke et al., 2022). Newly approved in 2022 is the combination of ICI therapy, including nivolumab and relatlimab. However, clinical trials demonstrated a similar toxicity profile with single agent Nivolumab and no decrease in quality of life (Tawbi et al., 2022).

Health-related quality of life (HRQoL) is an individual's mental and physical health perception based on variables of health risks and conditions, functional status, social support, and socioeconomic status (*HRQOL Concepts | CDC*, n.d.). Assessment of HRQoL in chronic diseases such as cancer is best achieved with the use of patient-reported outcome (PRO) instruments. PRO

instruments assess the patient experience, which may include symptoms of illness and therapy impacts on an individual's HRQoL, including function, activity, and relationships, providing data beyond the survival benefit of treatment.

ICIs are widely believed to be well-tolerated, without negative impact on HRQol (Boutros et al., 2021; Hall et al., 2019). However, emerging evidence suggests that with the expanded use of ICI therapy in the community, patients experience adverse events and severe toxicities that negatively impact HRQoL (Lai-Kwon et al., 2018; Mamoor et al., 2020; O'Reilly et al., 2020; Patrinely et al., 2020; Rogiers, Leys, De Cremer, et al., 2020; Rogiers, Leys, Lauwyck, et al., 2020). This discrepancy suggests limitations in our current assessment of HRQoL and symptoms in patients receiving ICI therapy and the need for disease- and treatment-specific PRO measures for use in this population.

A handful of studies have delineated the symptom experience among people living with melanoma, including survivors and patients receiving specific ICI therapies (i.e., pembrolizumab), but sparse data are available to understand the patient experience while undergoing ICI therapy (Fox et al., 2019; Laidsaar-Powell et al., 2019; Levy et al., 2019; Zwanenburg et al., 2022). While symptom presence and severity have been established in novel ICI clinical trials, descriptions of the symptom experience from the patient's perspective are lacking (Larkin et al., 2015; Long et al., 2016; Petrella et al., 2017; Schadendorf et al., 2016; Weber et al., 2017). Thus, the aim of this study was to explore the patient experience using descriptions of their words via interviews and evaluate and quantify their symptom burden and interference with the PRO instruments.

To our knowledge, this is the first study utilizing PRO instruments and participant interviews to understand the patients' lived experience of undergoing ICI therapy for advanced melanoma, including the most recently approved ICI regimen, nivolumab, combined with relatlimab.

Methods

This study, BS99-094_MOD022, was approved by the Internal Review Board of The University of Texas MD Anderson Cancer Center and The University of Texas Health Science Center at Houston, registration number IRB4 IRB00005015 and HSC-SN-20-0579. Participants were enrolled in a parent cross-sectional study for the purpose of collecting PRO data from patients receiving ICI therapy for melanoma. Participants were eligible for participation in qualitative interviews if they were (1) older than 18 years, (2) able to speak and read English, (3) currently receiving ICI therapy and within the first year of treatment, and (4) could provide informed consent to participate in a qualitative interview. A subset of participants was purposively selected from the parent study sample to obtain a diversity of characteristics representing the breadth of the ICI experience, such as age, sex, race, cancer stage, and presence of symptoms. After consenting to participate in a qualitative interview, participants were contacted by phone to allow for participant convenience, privacy, and the ability to record the interview for subsequent transcription. Recruitment continued until data saturation was achieved, defined as no new themes in three consecutive interviews (Parse, 2001).

Data collection

After informed consent and the participant completed PRO instruments for the parent study, subjects who agreed to participate in a qualitative interview were contacted by phone for their qualitative interviews. An interview guide was developed with input from melanoma medical oncologists and used for semi-structured qualitative interviews (Table 1). The interview guide featured open-ended questions that served as a guide during the interviews to capture the patient's lived experience. Open-ended questions were developed to capture not only the symptoms but also the degree of symptom burden and intensity and the impact of symptoms on the aspects of life such as work, relationships with others, daily functioning, financial burden, and ability to enjoy life. Questions developed were used to gain insight into the lived experience of diagnosis and participant thoughts on future therapy and outcomes. Interviews were audio-recorded, with participant consent, and professionally transcribed. After the interview, the interviewer (NJ) recorded field notes, documenting the circumstances of the interview. Transcripts were later verified and, if needed, corrected by the research team. Demographic, disease, and treatment data were collected from each participant's medical record. As part of the parent study, participants completed a modified version of the core MD Anderson Symptom Inventory (MDASI; (Cleeland, 2000) which included the core MDASI symptoms and symptoms believed to be relevant to the experience of patients with melanoma receiving ICI therapy and the Functional Assessment of Cancer Therapy-Melanoma (FACT-M) (Cormier et al., 2008) at the time of enrollment on

the parent study. Participants were not compensated for their completion of this sub-study.

The core MDASI a is a self-report multi-symptom PRO measure, with evidence of validity across cancer diagnoses that assesses symptom burden (the combined severity and functional impact of symptoms related to disease and treatment) in the past 24 hours (Cleeland, 2000). The core MDASI includes 13 symptoms and six interference items, measured on a 0-10 scale (0 = not present, 10 = as bad as you can imagine). The MDASI includes several subscales: a mean score is obtained for the symptom items, interference items, any additional module symptom items, and three interference subscales. The MDASI has evidence of content and construct validity in participants with cancer as well as sensitivity to capture symptomatic changes (Cleeland, 2000). The MDASI is structured to allow the addition of symptom items for disease- or treatment-specific MDASI modules. Utilizing a panel of experts in treating melanoma with ICI therapy, items from the MDASI symptom library were reviewed and agreed upon for inclusion in the Modified MDASI (Appendix A).

The FACT-M (Cormier et al., 2008) is a self-report 51-item questionnaire designed to measure four domains of HRQOL in participants with melanoma: physical, social, emotional, and functional well-being (Appendix B). There is evidence of reliability, convergent and divergent validity, criterion-related validity, and sensitivity to change (Cormier et al., 2008). The FACT-M is derived from the Functional Assessment of Cancer Therapy- General (FACT-G; Cella et al., 1993) and asks about the experience in the past seven days, are rated 0 ‘not at all’ to 4

‘very much’ with a total score of 0-172, and a higher score indicates better quality of life. The 27 items of the FACT-G are divided into four domains, Physical Well-Being (PWB, 7-items), Social and family Well-Being (SWB, 7-items), Emotional Well-Being (EWB, 6-items), and (Functional Well-Being, 7-items). The remaining items are split between the Melanoma Subscale (MS, 16-items) and the Melanoma Surgery Scale (MSS, 8-items).

Analysis

Descriptive statistics were calculated to describe the demographic and clinical characteristics of the study sample and the scores of the individual participants' severities of symptom and interference items and subscales of the Modified MDASI. All interview transcripts were imported into MAXQDA22 version 24 (VERBI GmbH, Berlin, Germany) for descriptive exploratory content analysis. This approach was inductive and iterative to understand the lived experience of having advanced melanoma and undergoing ICI therapy from the participant’s perspective. The research team (NJC, MW) created a list of identified symptoms and themes as the interviews were analyzed to describe how they related to the patient experience with ICI therapy and melanoma. The initial list of identified symptoms was reviewed by the research team (NJC, MW) and then collapsed into common categories after discussing whether those identified were unique or matched symptoms currently known and labeled. The data was presented to a few participants to validate the identified symptoms and themes. Participant quotes were extracted to exemplify the identified symptoms, and participant

descriptors were used to name the identified symptoms and further describe the content domain.

Results

Data saturation was reached upon completion of 19 interviews. Participants had a median age of 59.7 (range 34-82); two (10%) self-identified as Hispanic ethnicity; 16 (84%) self-identified as White (Table 2). Eight participants (42%) were receiving single-agent ICI nivolumab (n=7) or pembrolizumab (n=1). Four participants (30%) were receiving combination ipilimumab plus nivolumab, six (31%) were receiving combination relatlimab plus nivolumab, and one (5%) was participating in a blinded adjuvant trial of nivolumab or a combination of relatlimab plus nivolumab.

Heterogeneity of symptom experience and intensity

At the time of the interview, participants reported multiple symptoms related to therapy on the Modified MDASI, with the most severe (mean score 2 or greater on scale of 0-10) being fatigue (mean severity 2.79, SD 2.86), sleep disturbance (mean severity 2.39, SD 2.95), and lack of energy (mean severity 2.95, SD 2.91) (Table 3). Symptoms reported on the FACT-M (Table 4) as most severe (mean score >1.0) were lack of energy (mean severity 1.32, SD 0.95), worry condition will get worse (mean severity 1.26, SD 1.33), worry about dying (mean severity 1.22, SD 1.31), feel sad (mean severity 1.17, SD 1.15), fatigue (mean severity 1.16, SD 0.83) Seven symptoms were identified by at least 20% of informants during the interview, including distress (n=16, 84%), fatigue (n=13,

68%), rash or skin changes (n=10, 53%), pain (n=6, 32%), diarrhea (n=6, 32%), itching (n=5, 26%), and shortness of breath (n=4, 21%). Informant quotes representing these seven symptoms are presented in Table 5. Participants could occasionally attribute the fatigue and diarrhea to confirmed diagnosis or endocrine dysfunction such as thyroid, hypophysitis, adrenal insufficiency, and colitis, but less than 20% of participants used these labels in the interviews.

Three (16%) participants, each with metastatic disease, described a symptom and interference related to their melanoma disease, all of which resolved as ICI therapy was started. These symptoms included leg swelling due to a tumor (74-year-old male, metastatic, on combination therapy), jaw pain due to a tumor (34-year-old female, metastatic, on combination therapy), and lack of energy, ability to walk or breathe due to lung tumors (66-year-old male, metastatic, combination therapy), all interfering with activity and enjoyment of life for each participant. Unique symptoms disclosed in the interviews that were lacking on the available PRO instruments (Modified MDASI and FACT-M) included loss of all hair, increased thirst, altered sensation- described as “not-natural, a little like medicated, and like wow” (64-year-old male, combination therapy for metastatic disease), change in appearance, constipation and cough.

Symptom interference on the Modified MDASI was rated as most severe for general activity (mean severity 2.0, SD 2.3) and least severe for walking (mean severity 0.58, SD 1.47) (Table 3). Symptom interference on FACT-M was noted to be most impactful to emotional well-being (mean severity 18.21, SD 4.01) and least impactful to social/family well-being (mean severity 24.32, D 3.73)

(Table 4). Some interference related to therapy and symptoms was reported in the qualitative interview. Mood or emotions were impacted in nine (47%) of the participants, relations with other people were affected in five (26%) of the participants, and interference with activity in four (21%) participants. Quotes describing the interference are in Table 6.

In addition, nine themes (Table 7) were identified related to experiencing advanced melanoma, the impact of symptoms, and undergoing therapy.

Uncertainty of outcomes

The uncertainty of life after the diagnosis was the most common theme (n=12, 68%). It was generally described that the worst part was not knowing. “I feel a little more anxious than normal about what’s gonna happen in the future” (46-year-old female, neoadjuvant, combination therapy). There was also the anxiety and stress that was acutely worse before knowing the outcome of the scans. “What my anguish is not knowing what the future holds for me. What’s gonna happen? Is it gonna come back?” (51-year-old female, adjuvant, clinical trial combination vs. monotherapy). One participant also noted, “It was difficult to know if I was asking the right questions” (48-year-old female, metastatic, on combination therapy); there is so much information, and it is overwhelming. An 82-year-old male participant now on metastatic combination therapy noted that the stress of waiting to get an appointment with the doctor for treatment planning was highly distressing. A 52-year-old female undergoing adjuvant therapy noted, “If I don’t have symptoms, how will I know it spread, and will it be too late to

receive any kind of treatment." All participants acknowledged feeling a lack of control in the situation, contributing to distress.

Positive thoughts about ICI therapy

Regarding the therapy, most participants (n=11, 58%) had positive thoughts about their ICI therapy. One 66-year-old male participant was highly symptomatic from his metastatic disease burden, and "I was like, 'Oh, I don't know if I'm going to make it…we went on treatment, and within two weeks, I can't say I was hugely better, but I could tell I wasn't worse. I see [ICI therapy] as nothing short of a miracle" (66-year-old male, metastatic, combination therapy). "I think I've been very fortunate, very blessed to have been able to get the treatments and have them work so wonderfully" (67-year-old male, adjuvant, monotherapy). Multiple participants also highlighted the convenience of the short therapy times of single agent or nivolumab + relatlimab, which impacted less the other aspects of life (n=4). The 15 participants that did not report any physical interference from therapy noted how "they loved how they were still able to be active" (66 M, metastatic, combination therapy) and "everything is going well" (72-year-old male, metastatic, combination).

Expectations for the Success of Immunotherapy

Participants have belief in the successful outcome of therapy of their current ICI therapy (n=10, 53%) comprised of participants undergoing metastatic (n= 6) or adjuvant therapy (n= 4). When asked in the interview what they saw happening in the future with their melanoma, responses included, "I hope

nothing," "I feel like I'm going to beat this," and "see somewhat of a cure." This belief was tempered by one participant noting, "This may just be a lifelong thing I deal with and need occasional treatments in the future." And another participant stated, "Of course, I want to be cured, but as long as I'm not an invalid or where I'm a burden on society or my loved ones." Participants also expressed hope for the future, being grateful for the research previously done to create these advanced treatment options and access to doctors that provide this care.

Lack of Symptoms

Slightly less than the majority of participants noted a lack of symptoms while undergoing therapy (n=9, 47%). For example, one participant is quoted "because on any day I feel normal. I feel like there is nothing wrong like I shouldn't be in that category of technically sick people" (38-year-old female, metastatic, combination therapy). Other participants stated "I really haven't felt any, I've felt fine. I don't have any issues as far as any bowel issues or upset stomach, nausea. I don't have any of those things" (55-year-old female, metastatic, combination therapy) and "I get up and walk out [after the infusion of ICI], and it's as if nothing was ever done to me" (74-year-old female, metastatic, combination therapy). Participants either listed specific symptoms they did not have: nausea, upset stomach, appetite loss, weight loss, diarrhea, fever, aches, or pains, or they described it as feeling normal, able to work, able to exercise, or "I have a lot of energy" (55-year-old female, metastatic, combination therapy).

Coping

Participants described coping (n=8, 42%) in many ways. The two most common ways participants described coping were through accessing faith or the acknowledgment that “the situation could be worse.” One participant, a 70-year-old male undergoing combination therapy for metastatic disease, noted, “I'm ok, and I consider it's a blessing because I've seen people who have struggled with cancer, and they had a hard time coping with the pain and the perils that go along with it" (MC,). Another participant, a 67-year-old male undergoing adjuvant monotherapy, said, "It's so sad when I come here and see all these people that are suffering so badly, and I just kind of go, 'Man, you are a lucky son of a gun," you know because it could be like that for me." Another overreaching mechanism of coping was Faith. Participants acknowledged a "belief in God" or "I'm a big Jesus believer." This was combined with "I pray everything will be fine," "He has orchestrated each step so far and know he has other plans for me," or "God will make a way because he always has; we are going to figure this out." One participant said, "not that treatment was a positive experience, but it has been a smoother experience due to mental health support, I've been seeing a therapist about my experience" (34-year-old female, metastatic, combination therapy).

Sense of Control

While participants noted there was little, they could control regarding cancer and therapy, some aspects of life could be adjusted and empower them to have a sense of control. Diet and exercise were mentioned, but one participant noted how it could be confusing. “It would be good if providers acknowledged

that all the information out there isn't necessarily accurate and provided guidelines for best diet practices” (66 M, metastatic, combination therapy). Another participant reported how important attitude is and being positive can manifest positive outcomes, "I think attitude has a lot to do with it; I just have this great determination to beat this" (55-year-old female, metastatic, combination therapy). Similarly, "[reducing stress] can decrease inflammation and make your body hostile to cancer in your mind without ruining your mind and life" (66-year-old male, metastatic, monotherapy). Other participants reported now that they have melanoma, they are more aware of preventative practices, including applying sunscreen, wearing sun-protective clothing, and being more mindful of their skin and moles by seeking out healthcare sooner for a biopsy or evaluation.

Barriers to reporting symptoms

Some participants (n=5, 26%) acknowledged barriers to reporting symptoms to providers. Described as "I was coming to an appointment in a few days, and I didn't want to bother the team" (63-year-old male, adjuvant, single agent) and "It is sometimes difficult to get a hold of the team, so I just waited" (56-year-old female, metastatic, combination therapy). The communication delays or perceived inability to reach the provider team resulted in frustration for the participants, which further reduced their desire to try to discuss symptoms. Other participants noted that someone else in the family had the same symptoms, so I wasn't sure if it was related, and they didn't want to bother the provider and thought it would get better. A few participants noted the concern of being a burden to family and the healthcare team.

Shock of the diagnosis

The impact of the diagnosis of melanoma was reported by five participants (26%). One participant noted, "I was devastated [by the diagnosis]; I had just gone in to get a regular eye exam" (70-year-old male, metastatic, combination therapy). Another participant noted, "Everyone was surprised it was a melanoma because it had no characteristics of a melanoma" (55-year-old female, adjuvant, monotherapy). Participants described themes of anxiety, concern for their future, and concern for their family's future while describing the shock. Participants noted wanting to do whatever it takes to improve their length of survival.

Navigating the Healthcare system

Navigating the healthcare system (n=5, 26%) included the impact on time, finances, and communication with the oncology team. Participants noted the financial implications that came with the diagnosis, such as copays, parking, travel, missing some work, and the frequency of visits. Communication for the participants was noted for some to be very positive, while some couldn't always quickly get in touch with their care team, or the phone system was too complicated. One participant noted, "The only problem I have is I don't really know what's gonna happen until I see it in myChart. My only complaint is I don't know ahead of time." (66-year-old female, metastatic, monotherapy). A 51-year-old female on an adjuvant clinical trial monotherapy vs. combination therapy said, "When we go to see the doctor and even my research nurse, it's never really been touched about there are support groups, and we know it's not just the disease; its everything that comes with it." This is echoed by other participants

reporting that they rely entirely on their medical provider to give them the best information and treatment options.

Discussion

Here, we provide insight into the patient's perception of diagnosis with advanced melanoma and the impact of undergoing ICI therapy, including a description of the symptoms experienced and the impact of symptoms on functioning. Our findings were similar to those of Ala-Leppilampi et al. (2020), who clustered their conclusions into eight major themes. Participants of each study were thankful for the innovation of ICI therapy, grateful to have access to this option, a belief that it will work, felt it essential to be positive and were hopeful for the future. Both studies noted the "uncertainty" around therapy outcomes and what will be in the future. Ala-Leppilampi et al. (2020) described a theme of "reframing the meaning and severity of side effects" with similar statements of issues discerning if symptoms were from the therapy, cancer, or aging; but also noted participants found comfort in the side effects as they felt it meant it was working which was not described by any of the 19 participants in this study. Another difference is while participants in this study were grateful for their medical team, they also discussed some of the barriers to reporting symptoms and navigating the health system; negatives about therapy or healthcare were not presented in the study or possibly not addressed by the participants with Ala-Leppilampi et al. (2020). Participants were shocked by their diagnosis of advanced melanoma and felt an unclear prognosis with complexity due to an uncertain disease trajectory and ICI outcomes (Fox et al., 2019).

Uncertainty was a prominent theme and source of distress for the participants in the study by Fox (2019), which is consistent with the findings of this study.

In our sample, participants acknowledged the importance of medical advances and opportunities to treat advanced melanoma and possibly experience a long-term durable response. However, the uncertainty of outcomes weighed heavily on them, consistent with other studies (Levy et al., 2019; Zwanenburg et al., 2022). The participants that reported minimal symptom burden an minimal impact on HRQoL while undergoing therapy, some even noting how normal they felt was consistent with other studies (Boekhout et al., 2021; Boutros et al., 2021; Hall et al., 2019; Hemstock et al., 2020; Larkin et al., 2019). A few participants reported severe toxicities from therapy, such as colitis or hypophysitis, that caused a negative impact on their HRQoL. Other participants endorsed emotional lability, sadness, and anxiety from the diagnosis of advanced melanoma and undergoing ICI therapy, consistent with previous data (Milne et al., 2020; Rogiers, Leys, De Cremer, et al., 2020; Rogiers, Leys, Lauwyck, et al., 2020).

PRO data has burgeoned into an essential endpoint of clinical trials in oncology patients, providing an understanding of the depth and tolerance of treatment regardless of survival outcome (Basch et al., 2014). This study further endorsed the need to use disease- and treatment-specific PRO measures to capture the presence of symptoms' severity and interference accurately (Atkinson et al., 2016; Basch et al., 2009; Laugsand et al., 2010). Existing PRO instruments ask general questions about emotional well-being and anxiety, but

the frequency to which anxiety, concern for the future, and lack of control surrounding the diagnosis and therapy noted in the qualitative interview expose an area for further research and the need for innovative interventions to address distress. Though not the purpose of this study, our results provide evidence to support the creation of an ICI-specific PRO instrument for patients with advanced melanoma.

There are limitations to this study. While the interview guide used was crafted to reduce bias, the interviewer answered clarifying questions, but tone of voice, and recall bias for the interviewee could contribute to the possible introduction of bias to this study. The participants in this study were well-educated with at least some college level education, a majority were White and female, and all were followed at a comprehensive cancer care center in an academic setting. Due to these reasons, this sample may not accurately represent the general population of patients with advanced melanoma undergoing ICI therapy. Though it worth noting that White is the overwhelming demographic of melanoma secondary to incidence patterns (*Melanoma Skin Cancer Statistics*, n.d.).

Conclusion

Communication is key, educating patients that each person will have a unique and heterogenous experience while undergoing ICI therapy that could include toxicities with intense symptoms and HRQoL interference or be asymptomatic—reminding patients that they are not a burden by reporting their symptoms and that it is important to address symptoms early to reduce the

negative impact. Nurses and providers must be mindful that patients may not disclose symptoms unless directly asked; therefore, a PRO instrument and a thorough review of systems are imperative to capture the patient's symptom burden and interference. Lastly, the emotional burden of a melanoma diagnosis, undergoing therapy, and the uncertainty of the outcomes is pervasive for these participants and warrants further research of the best instrument for assessment and interventions for management.

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Table 1

Interview Guide

1. What is it like for you to undergo treatment with ICI [specific name] for your advanced melanoma?
2. Potential additional probe questions if patient does not describe spontaneously
    a. What symptoms are you experiencing?
    b. How is (ask with name of each individual symptom mentioned by patient, one symptom at a time) impacting your daily activities?
        - Have all the important aspects of your ICI experience been described?
        - What was it like for you when you first had melanoma and started ICI?
3. Potential additional probe questions if patient does not describe spontaneously
    a. What symptoms were you experiencing? If you are having trouble eliciting symptoms, ask the patient, "What symptoms did you notify the doctor about while undergoing ICI therapy?"
    b. How did ICI therapy impact your daily activities?
        - What other symptoms have you experienced that were related to melanoma or ICI therapy?
4. Potential additional probe questions if patient does not describe spontaneously
    a. What symptoms did you experience when you were having treatment with ICI?
    b. What treatment or procedure were you receiving when these symptoms occurred?
    c. How did (ask with name of each individual symptom mentioned by patient, one symptom at a time) impact your daily activities?
        - Have all the important aspects of experiencing therapy with ICI been described?
        - What do you see happening in the future with your melanoma?
5. Are there any other aspects of experiencing treatment with ICI that you would like to tell me about?
6. Is there anything else important about having advanced melanoma that you would like to tell me

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Note. Questions asked during semi-guided interview

Table 2

Demographics

Characteristics	**Participants N (%)**
Age	
Median (range)	59.7 (34-82)
Sex	
Male	8 (42)
Female	11 (58)
ECOG Performance	
0	12 (63)
1	7 (37)
Race	
White	16 (84)
Black	1 (5)
Asian	1 (5)
Hispanic	1 (5)
Ethnicity	
Hispanic or Latino	2 (10)
Not Hispanic or Latino	17 (90)
Marital Status	
Married	16 (84)
Single	1 (5)
Divorce	1 (5)
Widowed	1 (5)
Education	
Some college	5 (26)
College Graduate	8 (42)
Graduate/Professional Training	6 (32)
Employment status	
Employed full time	11 (58)
Employed part time	2 (10)
Retired	5 (26)
Unemployed	1 (5)

Table 2

Continued

Characteristics	**Participants N (%)**
Therapy	
Pembrolizumab	1 (5)
Nivolumab	7 (37)
Ipilimumab + Nivolumab	4 (30)
Nivolumab + relatlimab (N+R)	6 (31)
Blinded Clinical trial with Nivolumab vs N+R	1 (5)
Timing of therapy	
Adjuvant	5 (26)
Neoadjuvant	1 (5)
Metastatic	13 (68)
Disease Stage	
Stage II	1 (8)
Stage III	6 (33)
Stage IV	12 (58)
Clinician ROS	
Symptoms present	16 (84)
Symptoms not present	3 (16)

Table 3

MD Anderson Symptom Inventory symptom item prevalence and severity in rank order by mean severity (n=19)

Measure items and scores		Score- Mean (SD)	Median (min, max)
Core items	Fatigue	2.79 (2.86)	1 (0, 9)
	Sleep	2.39 (2.95)	1 (0, 9)
	Distressed	1.89 (2.36)	0 (0, 7)
	Dry mouth	1.84 (2.57)	1 (0, 8)
	Feeling drowsy	1.74 (2.45)	1 (0, 8)
	Remembering things	1.63 (2.06)	1 (0, 6)
	Pain	1.58 (3.01)	0 (0, 10)
	Feeling sad	1.11 (2.08)	0 (0, 7)
	Shortness of breath	1.05 (2.30)	0 (0, 8)
	Nausea	1.00 (2.38)	0 (0, 8)
	Lack of appetite	0.95 (1.68)	0 (0, 7)
	Numbness or tingling	0.89 (1.20)	0 (0, 3)
	Vomiting	0.58 (2.29)	0 (0, 10)
Melanoma Specific Items	Lack of energy	2.95 (2.91)	2 (0, 8)
	Itching	1.95 (2.55)	1 (0, 10)
	Rash or skin changes	1.84 (2.79)	1 (0, 10)
	Malaise/not feeling well	1.79 (2.74)	0 (0, 8)
	Eye problems	1.74 (2.00)	1 (0, 5)
	Skin problems	1.63 (2.57)	0 (0, 8)
	Irritability	1.58 (2.29)	0 (0, 7)
	Joint stiffness/soreness	1.53 (1.93)	1 (0, 7)
	Headache	1.32 (2.36)	0 (0, 7)
	Problems with feeling cold	1.32 (1.77)	0 (0, 5)
	Fever or chills	1.11 (2.83)	0 (0, 9)
	Muscle weakness	1.11 (1.94)	0 (0, 6)
	Muscle soreness	1.11 (1.73)	0 (0, 6)
	Problems with concentrating	1.05 (1.96)	0 (0, 8)
	Weakness in arms or legs	0.94 (1.51)	0 (0, 5)
	Problems with feeling hot	0.89 (1.49)	0 (0, 4)
	Issues with balance	0.68 (1.06)	0 (0, 3)
	Dizziness	0.61 (0.98)	0 (0, 3)
	Mouth/throat sores	0.53 (1.43)	0 (0, 6)
	Pain in the abdomen	0.47 (1.12)	0 (0, 4)
	Problem with the teeth or gums	0 (0.0)	0 (0, 0)

Table 3

Continued

Measure items and scores		**Score- Mean (SD)**	**Median (min, max)**
Interference Item	General activity	2.00 (2.30)	1 (0, 7)
	Mood	1.37 (2.19)	0 (0, 7)
	Work	1.84 (2.09)	1 (0, 6)
	Relations with others	1.16 (1.92)	0 (0, 6)
	Walking	0.58 (1.47)	0 (0, 6)
	Enjoyment of Life	1.11 (1.82)	0 (0, 6)
Composite Scores			
	Core	1.48 (1.61)	0.77 (0, 6.31)
	Melanoma	1.25 (1.37)	0.95 (0, 5)
	Total symptom	1.34 (1.41)	0.79 (0, 5.5)
	Interference	1.34 (1.71)	0.83 (0, 5.83)
	WAW	1.47 (1.74)	1.0 (0, 6.33)
	REM	1.21 (1.86)	0 (0, 6)

Note. WAW= **w**alking, general **a**ctivity, **w**ork; REM= **r**elationships with others, **e**njoyment of life, **m**ood

Table 4

Functional Assessment of Cancer Therapy - Melanoma Symptom items in rank order by mean and subscale scores

		Mean (SD)	Median (min, max)
Symptom Item (score 0-4)			
	Range of Motion [1]	2.83 (1.69)	4 (0, 4)
	Sleeping [1]	2.79 (1.03)	3 (1, 4)
	Appetite [1]	2.63 (1.53)	3 (0, 4)
	Lack of energy	1.32 (0.95)	1 (0, 4)
	Worry my condition will get worse	1.26 (1.33)	1 (0, 4)
	Worry about dying	1.22 (1.31)	1 (0, 4)
	Feel sad	1.17 (1.15)	1 (0, 4)
	Fatigue	1.16 (0.83)	1 (0, 3)
	Feel nervous	0.89 (0.94)	1 (0, 3)
	Difficulty remembering/concentrating	0.68 (0.89)	0 (0, 3)
	Pain at surgical site	0.68 (0.99)	0 (0, 4)
	Skin changes	0.68 (1.00)	0 (0, 3)
	Headaches	0.63 (0.83)	0 (0, 3)
	Aches and pains in bones	0.58 (1.07)	0 (0, 4)
	Overwhelmed by condition	0.58 (0.90)	0 (0, 3)
	Shortness of Breath	0.47 (0.91)	0 (0, 3)
	Pain	0.47 (1.02)	0 (0, 4)
	Numbness at surgical site	0.47 (0.91)	0 (0, 3)
	Swelling/cramps stomach	0.42 (0.77)	0 (0, 2)
	Worry about appearance of surgical scars	0.37 (0.68)	0 (0, 2)
	Feel ill	0.32 (0.58)	0 (0, 2)
	Nausea	0.32 (0.58)	0 (0, 2)
	Fevers	0.21 (0.71)	0 (0, 3)
	Swelling at melanoma site	0.16 (0.38)	0 (0, 1)
	Blood in stool	0 (0)	0 (0, 0)
Subscale (range)		Mean (SD)	Median (min,max)
	Physical well-being (0-28)	23.79 (4.29)	25 (11, 28)
	Social/Family well-being (0-28)	24.32 (3.73)	25 (13, 28)
	Emotional well-being (0-24)	18.21 (4.01)	19 (11, 24)
	Functional well-being (0-28)	22.21 (4.52)	22 (11, 28)
	Melanoma Subscale (0-64)	54.84 (6.48)	57 (37, 62)
	Melanoma surgery (0-32)	29.42 (2.43)	29 (25, 32)

Note. 1= reverse scored

Table 4

Continued

Composite Scores (range)		Mean (SD)	Median (min,max)
	FACT-M TOI (0-120) FACT-G total (0-108) FACT-M total (0-172)	100.84 (12.75) 88.53 (11.55) 143.37 (16.29)	101 (63, 117) 90 (61, 108) 145 (102, 168)

Note. FACT-M= Functional Assessment of Cancer Therapy- Melanoma, TOI= trial outcome index, G= general

Table 5

Symptoms and interference identified by informants during the qualitative interviews

Item		**N(%)**
Symptom	Distress	16 (84.2)
	Fatigue	13 (68.4)
	Rash or skin changes	10 (52.6)
	Pain	6 (31.6)
	Diarrhea	6 (31.6)
	Itching	5 (26.3)
	SOB	4 (21.1)
	Sweating	3 (15.8)
	Chills	3 (15.8)
	Muscle soreness	3 (15.8)
	Joint stiffness/soreness	3 (15.8)
	Feeling sad	3 (15.8)
	Dry mouth	3 (15.8)
	Irritability	2 (10.5)
	Numbness	2 (10.5)
	Nausea	2 (10.5)
	Problems with teeth or gums	2 (10.5)
	Change in appearance*	2 (10.5)
	Issue with remembering things	2 (10.5)
	Disturbed sleep	2 (10.5)
	Dizziness	1 (5.3)
	Eye problems	1 (5.3)
	Headache	1 (5.3)
	Malaise	1 (5.3)
	Feeling hot/hot flashes	1 (5.3)
	Loss of all hair*	1 (5.3)
	Increased thirst*	1 (5.3)
	Swelling of legs, hands, feet, abdomen	1 (5.3)
	Constipation*	1 (5.3)
	Altered sensation/non-natural state*	1 (5.3)
	Cough*	1 (5.3)
Interference	Lack of Physical Interference	15 (79.0)
	Mood	9 (47.4)
	Relations with other people	5 (17.2)
	Activity	4 (21.1)

Note. (*) =Not an item on MD Anderson Symptom Inventory or Functional Assessment of Cancer Therapy-Melanoma

Table 6

Informant quotes about the Symptoms and interference reported by at least 20% of participants in the interview

Symptom	Quote
Distress (n=16)	1. "I'm a planner and [melanoma isn't like that], you're just kind of always waiting. I [noted when it recurred the second time] 'I guess we are just gonna play chase the melanoma now'. So it's unsettling [not knowing]." (66 F, metastatic, monotherapy) 2. "I'm sad that this is a part of my life that I never expected, and I'm sad that my children have to live through it." (48 F, metastatic, combination therapy)
Fatigue (n=13)	1. "I had a bad fever, chills and had absolutely no energy. I would have to sit down in the middle of the shower, and getting out after taking a shower, I was sweating, and I didn't even know that was possible. I just felt completely drained" (49 F, metastatic, monotherapy) 2. "the fatigue makes me sit a little bit longer than I would generally, but overall, I'm still able to function" (48 F, metastatic, combination therapy)
Rash or skin changes (n=10)	1. "There is a new white spot on my nose, they told me it a side effect and I don't have to worry about it" (72 M metastatic, monotherapy) 2. The symptoms are mostly… rash and just dryness" (46 F, neoadjuvant, combination therapy)
Pain (n=6)	1. "My neck pain, I can't look up, I can't look down well. I can't turn and I'm in pain" (82 M, metastatic, combination therapy). 2. "I was so crippled [with joint pain], I couldn't move. I was like a thousand-year-old man, I couldn't even get out of my wife's care" (66 M, metastatic, combination therapy)
Diarrhea (n=6)	1. "I was so sick with colitis and bloody diarrhea. Then all hell broke loose [and I had surgery] to remove part of my large intestine" (71 F, metastatic, monotherapy) 2. "Every now and then I'll have explosive diarrhea. But it seems like the next day I'm fine" (66 F, metastatic, monotherapy)

Note. F= female, M=male

Table 6

Continued

Symptom		**Quote**
	Itching (n=5)	1. Now, the worst side effect for me was the itching of the skin, which is not much to complain about, but your skin documents, this is more than just treatment there is inflammation." (66 M, metastatic, combination therapy) 2. "the itching is, it's kind of strange, it is mostly on my back of my arms and on the top of my head. It's just a—it's not an annoyance, it's more of just something that happens every now and then." (42 M, adjuvant, monotherapy).
	Shortness Of Breath (n=4)	1. "I have a little shortness of breath at times. They prescribed me an inhaler as needed" (72 M metastatic, monotherapy) 2. "I mean I still get a little more winded and I get a little more tired than I would prior to having the infusions" (70 M, metastatic, combination therapy)
Interference		**Quote**
	Lack of physical interference (n=15)	1. "No, I still go like I used to go, [activities everyday next week with her grandchildren or volunteering], it hasn't slowed me down any" (74 F, metastatic, monotherapy) 2. "I mean, I feel normal, except on paper, the exams and stuff, there is melanoma there" (38 F, metastatic, combination therapy)
	Mood (n=9)	1. "I've just got to do my living and quit worrying about dying" (66 F, metastatic, monotherapy) 2. "I just the unknown of what's gonna happen and the anxiety that goes with that is challenging" (42 M, adjuvant, monotherapy)
	Relations with other people (n=5)	1. "I don't want my children's memories of me to be sick or sad" (48 F, metastatic, combination therapy) 2. "my wife came with me early on [for treatments], so it disrupted her life too" (67 M, adjuvant, monotherapy)
	Activity (n=4)	1. "It is just hard to motivate myself to do the extra things, like go to the gym and see friends [due to the fatigue]" (34 F, metastatic, combination therapy) 2. "I'm just exhausted the day after treatment" (38 F, metastatic, combination therapy)

Note. M= male, F= female

Table 7

Themes related to the experience of immune checkpoint inhibitor therapy for advanced melanoma

Theme	N (%)	Quotes
Living with Uncertainty	13 (68.4)	1. “What my anguish is not knowing what the future holds for me. What’s gonna happen? Is it gonna come back?” (51 F, adjuvant, clinical trial combination therapy vs monotherapy) 2. “I feel a little more anxious than normal about what’s gonna happen in the future” (46 F, neoadjuvant, combination therapy)
Positive thoughts about immune checkpoint (ICI) therapy	11 (57.9)	1. “I was like, ‘Oh, I don’t know if I’m gonna make it…we go onto treatment and within two weeks I can’t say I was hugely better, but could tell I wasn’t worse. I see [ICI therapy] as nothing short of a miracle” (66 M, metastatic, combination therapy) 2. “I think I’ve been very fortunate, very blessed to have been able to get the treatments and have them work so wonderfully” (67 M, adjuvant, monotherapy)
Expectations for success of therapy	10 (52.6)	1. “As far as I know, this is all going away, [all the tests I’m doing are fine] So I guess I’m gonna be healed” (59 M, adjuvant, monotherapy) 2. “I think that once the medication takes hold in my boy, that hopefully it will do something with my cancer. It will take care of the caner in my leg.” (74 M, metastatic, combination therapy)
Lack of Symptoms	9 (47.4)	1. “Because on any day I feel normal. I feel like there is nothing wrong, like I shouldn’t be in that category of technically sick people” (ST, 38 F, metastatic, combination therapy) 2. “I really haven’t felt any, I’ve felt fine. I don’t have any issues as far as any bowel issues or upset stomach, nausea. I don’t have any of those things.” (55 F, metastatic, combination therapy)

Note. F= female, M = male

Table

Continued

Theme	N (%)	Quotes
Coping	8 (42.1)	1. “Not that treatment was a positive experience, but it has been a smoother experience due to mental health support, I’ve been seeing a therapist about my experience” (34 F, metastatic, combination therapy). 2. “I try to go out of my way to not look like I have melanoma, stage IV cancer. I don’t want to look at the mirror every day and be reminded that I have stage IV cancer” (49 F, metastatic, monotherapy)
Sense of control	5 (26.3)	1. I think diet, doing it in a way you can do it every day without a lot of pain and agony. And [reducing] the lack of stress/inflammation, which cancer wants to thrive on, making your body hostile to cancer in your mind without ruining your mind” (66 M, metastatic, combination therapy) 2. “I think attitude has a lot to do with it, I just have this great determination to beat this” (55 F, metastatic, combination therapy)
Barriers to reporting symptoms to provider	5 (26.3)	1. “I’m usually pretty hesitant to notify doctors until it’s really bad, just because I feel like there’s—its hard to know because the side effects that you hear about and that they tell you about those are all the same things I would have normally” (46 F, neoadjuvant, combination therapy). 2. “I figured I was coming here anyway, and so you might as well wait. And you know, I’ll be honest with you. Sometimes it more difficult to get in touch with people here than I think the team would like to think it is” (67 M, adjuvant, monotherapy)
Shocked by the diagnosis	5 (26.3)	1. “I was devastated [by the diagnosis], I had just gone in to get a regular eye exam” (70 M, metastatic, combination therapy) 2. “everyone was surprised it was a melanoma because it had not characteristics of a melanoma” (55 F, adjuvant, monotherapy)
Navigating the Healthcare system	5 (26.3)	1. “The only problem I have is I don’t really know what’s gonna happen until I see it in myChart. My only complaint is I don’t know ahead of time.” (66 F, metastatic, monotherapy) 2. “When we go to see the doctor and even my research nurse, it’s never really been touched about there are support groups, and we know it’s not just the disease; its everything that comes with it” (51 F, adjuvant, clinical trial combination therapy vs monotherapy)

Note. F= female, M = male

Appendix A

Sample of the Modified MDASI

MDASI-Modified

Please complete the survey below.

Thank you!

MDASI Completion Date: _____

M. D. Anderson Symptom Inventory-Modified

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours.

Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your pain at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your fatigue (tiredness) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your nausea at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your disturbed sleep at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being distressed (upset) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your shortness of breath at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with remembering things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with lack of appetite at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling drowsy (sleepy) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

10. Your having a dry mouth at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling sad at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your vomiting at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your numbness or tingling at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your dizziness at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your eye problems at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your fever or chills at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your headache at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your irritability at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your issues with balance at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your itching at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your joint stiffness/soreness at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your lack of energy at its WORST?	○	○	○	○	○	○	○	○	○	○	○
23. Your malaise/not feeling well at its WORST?	○	○	○	○	○	○	○	○	○	○	○
24. Your mouth/throat sores at its WORST?	○	○	○	○	○	○	○	○	○	○	○
25. Your muscle soreness/cramping at its WORST?	○	○	○	○	○	○	○	○	○	○	○
26. Your muscle weakness at its WORST?	○	○	○	○	○	○	○	○	○	○	○
27. Your pain in the abdomen at its WORST?	○	○	○	○	○	○	○	○	○	○	○
28. Your problem with teeth or gums at its WORST?	○	○	○	○	○	○	○	○	○	○	○
29. Your problems with concentrating at its WORST?	○	○	○	○	○	○	○	○	○	○	○
30. Your problems with feeling cold at its WORST?	○	○	○	○	○	○	○	○	○	○	○
31. Your problems with feeling hot at its WORST?	○	○	○	○	○	○	○	○	○	○	○
32. Your rash or skin changes at its WORST?	○	○	○	○	○	○	○	○	○	○	○

33. Your skin problems at its WORST?	○	○	○	○	○	○	○	○	○	○	○
34. Your weakness in arms or legs at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Did you intentionally leave any items blank? ○ Yes ○ No

If yes, please continue to the next page.

If no, please go back and finish the previous items.

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours?

Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
35. General activity?	○	○	○	○	○	○	○	○	○	○	◉
36. Mood?	○	○	○	○	○	○	○	○	○	○	○
37. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
38. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
39. Walking?	○	○	○	○	○	○	○	○	○	○	○
40. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

Did you intentionally leave any items blank? ○ Yes ○ No

If yes, please continue to the next page.

If no, please go back and finish the previous items.

Form Completion

How was this form completed?

○ By the participant
○ By the study coordinator (over the phone or by interview)

Please draw signature with mouse or finger

Appendix B

Sample of the FACT-M

FACT-M (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
M1	I have pain at my melanoma site or surgical site	0	1	2	3	4
M2	I have noticed new changes in my skin (lumps, bumps, color(colour))	0	1	2	3	4
M3	I worry about the appearance of surgical scars	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
ITU4	I have to limit my physical activity because of my condition	0	1	2	3	4
Aa10	I get headaches	0	1	2	3	4
Hsp3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
M5	I have aches and pains in my bones	0	1	2	3	4
M6	I have noticed blood in my stool	0	1	2	3	4
ITU3	I have to limit my social activity because of my condition	0	1	2	3	4
MS8	I feel overwhelmed by my condition	0	1	2	3	4
M8	I isolate myself from others because of my condition	0	1	2	3	4
M9	I have difficulty thinking clearly (remembering, concentrating)	0	1	2	3	4
H7	I feel fatigued	0	1	2	3	4

FACT-M (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	At the site of my melanoma surgery:	Not at all	A little bit	Some-what	Quite a bit	Very much
M10	I have swelling at my melanoma site	0	1	2	3	4
M11	I have swelling as a result of surgery	0	1	2	3	4
M12	I am bothered by the amount of swelling	0	1	2	3	4
M13	Movement of my swollen area is painful	0	1	2	3	4
M14	Swelling keeps me from doing the things I want to do	0	1	2	3	4
M15	Swelling keeps me from wearing clothes or shoes I want to wear	0	1	2	3	4
M16	I feel numbness at my surgical site	0	1	2	3	4
M17	I have good range of movement in my arm or leg	0	1	2	3	4

Evaluating the patient experience of symptom burden while undergoing Immune Checkpoint Inhibitor (ICI) therapy for advanced melanoma compared to clinician perception: A quantitative study.

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Abstract

Purpose is to describe the symptom experience from the patient's perspective and how it relates to the quality of life among patients undergoing immune checkpoint inhibitors (ICIs) for advanced melanoma across the treatment trajectory. Another aim is to evaluate the concordance between symptoms communicated during a follow-up visit and reported via patient-reported outcome (PRO) measure.

Methods: This is a single-center, cross-sectional study of patients with advanced melanoma within their first year of ICI therapy. Participants completed two PRO instruments, the FACT-M, and the Modified MDASI. The clinical review of systems was captured from the electronic health record from the visit in which the PRO instruments were completed to assess the degree of matching.

Results: All 60 participants reported at least one symptom with each PRO instrument. Most common on the Modified MDASI was lack of energy (N=43, 72%), fatigue (n=42, 71%), feeling drowsy (n=35, 60%), joint stiffness/soreness (n=34, 57%), disturbed sleep (n=33, 56%), dry mouth (n=32, 53%), and itching (n=30, 50%). The most common on FACT-M was fatigue (n=49, 82%), lack of energy (n=46, 77%), worry that the disease would get worse (n=38, 63%), worry about dying (n=32, 54%), and feeling sad (n=32, 54%). More than 50% of participants reported interference with working (n=32, 53%) and general activity (n=33, 55%). Participants reported three or more symptoms on the PRO instrument than the number documented by the clinician's ROS in the EHR.

Conclusion: Having patients complete a PRO instrument with clinical ROS and assessment can provide a complete picture of symptom burden and patient experience while undergoing ICI. Further research is needed to finalize a melanoma ICI-specific instrument.

Keywords: Melanoma, immunotherapy, symptoms, patient-reported

Introduction

Immune checkpoint inhibitors (ICIs) are considered the standard of care for managing multiple types of cancer but were first approved by the Food and Drug Administration (FDA) for use in patients with melanoma due to their meaningful clinical benefit to patients (Twomey & Zhang, 2021; Vaddepally et al., 2020). ICIs utilize the adaptive immune system to elicit anti-tumor activity and eliminate cancer cells by interrupting immune checkpoints using anti-CTLA-4, anti-PD-1, and anti-PD-L1 antibodies, blocking inhibitory interactions between T-cells and other cells and tissues, allowing for unchecked T-cell activation (Furue & Kadono, 2016; Jeurling & Cappelli, 2020; Topalian et al., 2015). Comprehensive cancer care includes assessing and managing toxicities, which are fundamentals of oncology care, as participants undergo therapy for their advanced melanoma (American Society of Clinical Oncology & European Society for Medical Oncology, 2006; Cleeland, 2000). This is particularly important when the toxicities do not follow a standard trajectory of presentation, such as immune-mediated adverse events while receiving ICIs (Chan & Bass, 2020).

The experience of any-grade toxicities among those receiving ICIs ranges from 66% to 92%, but the rate of Grade 3 or 4 toxicities is 20-55% (Bottomley et al., 2021; Dalle et al., 2021; Kennedy & Salama, 2020; Larkin et al., 2015; Luke et al., 2022; O'Reilly et al., 2020; Patrinely et al., 2020). The most common immune-related adverse events (irAEs) are dermatitis, pruritis, fatigue, colitis, pneumonitis, and endocrinopathies (Thompson et al., 2020). Most irAEs can be treated with a delay or cessation of therapy or supportive treatments such as

steroids or immunosuppressive agents but can be lethal if not recognized and appropriately treated (Furue et al., 2018; Haanen et al., 2022; Postow, 2022). Symptom burden from ICI therapy is known to be heterogenous and can impact patients at different time points while undergoing treatment (Abdel-Wahab et al., 2016). Due to the dynamic nature of melanoma and its symptoms, it is paramount to involve the patient in every aspect of their care, which may be challenging given the current lack of disease- and treatment-specific instruments to assess their experience.

Clinical experience suggests that patients undergoing ICI therapy will experience toxicity, but overall, patients report little impact on health-related quality of life (HRQoL). The majority of published data regarding toxicities and HRQoL is from clinical trials utilizing one or both generic patient-reported outcome (PRO) instruments, the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) or the EuroQol (EQ-5D), to assess this outcome (Coens et al., 2017; Long et al., 2016; Petrella et al., 2017; Schadendorf et al., 2017; Weber et al., 2017). These disease- and treatment-agnostic PRO instruments have been validated in oncology patients undergoing chemotherapy or radiation, not ICI therapy, and are not specific to the melanoma population (Aaronson et al., 1993; Groenvold et al., 1997). A few studies outside of randomized controlled clinical trials, completed HRQoL assessment with a melanoma-specific measure, the Functional Assessment of Cancer Therapy-Melanoma (FACT-M; Cormier et al., 2008). This measure was also developed before the addition of ICI therapy as

melanoma standard-of-care practice (Boekhout et al., 2021; Tolstrup et al., 2022).

Capturing PROs from patients with melanoma receiving ICI therapy will allow providers and researchers to gain a more clinically meaningful understanding regarding specific impacts on HRQOL related to disease and treatment (Holch et al., 2016; Mooney et al., 2017). There are known discrepancies between what patients experience per PROs and clinicians' perception of symptoms and their burden (Atkinson et al., 2016; Basch et al., 2009). However, research shows that routine PRO assessment improves patient-provider communication and patient HRQoL (Kotronoulas et al., 2014; Mooney et al., 2017; Velikova et al., 2004) and improves clinical outcomes and survival rates (Basch et al., 2017; Denis et al., 2019). Thus, this study aims to evaluate the symptom experience of patients receiving ICI for the treatment of melanoma utilizing PRO measures.

Methods

This study was approved by the Internal Review Boards of The University of Texas MD Anderson Cancer Center (IRB00005015) and The University of Texas Health Science Center at Houston (HSC-SN-20-0579). Participants were enrolled in a cross-sectional study to collect PRO and qualitative data from patients receiving ICI therapy for melanoma. To explore the congruency between symptoms rereported by the participants on the PRO instruments and those documented by the clinicians (nurse, advanced practice provider, and/or

physician) in the electronic health record (EHR). The clinicians did not administer the PRO instrument, nor were they requested to do their ROS differently for this study. After completing the PRO instruments, participants were asked, "Do you feel the surveys adequately captured your treatment experience?" A subset of participants in this study completed individual qualitative interviews; those findings are reported in a separate study pending publication.

Sample

Participants were diagnosed with advanced melanoma and actively receiving ICI therapy at the Melanoma Medical Oncology Department at The University of Texas MD Anderson Cancer Center (MDACC) between September 1, 2022, and January 31, 2023. Participants were eligible to participate in the study if they were 18 years or older, could speak and read English, were currently receiving ICI therapy, were within the first year of ICI treatment, and could provide informed consent to participate. Participants were screened and approached in the melanoma clinic or on the phone if having a telemedicine visit. Sampling was purposive to obtain diversity in characteristics such as age, sex, race, stage, and presence of symptoms on the review of systems to garner the breadth of the ICI experience. All participants provided verbal and written consent. Demographics were collected from the EHR or verbally from the participant.

PRO Instruments and Data Collection

After providing consent, participants completed PROs with either an electronic tablet at the clinic visit or an electronic link via Research Electronic Data Capture (REDCap, Harris et al., 2009, 2019) to the participants' confirmed email. Instruments were completed within 72 hours of the follow-up visit. A reminder email was sent 24 hours after the initial email if the PROs had not been completed.

Measures

The core MD Anderson Symptom Inventory (MDASI) is a PRO instrument with evidence of validity in multiple cancer diagnoses. It evaluates various symptoms, intensity, and interference in the previous 24-hour period (Cleeland, 2000). The core MDASI is comprised of 13 symptom items and six interference items. All items are measured on a 0-10 scale (0 = not present, 10 = as bad as you can imagine). In this study, the MDASI was scored using six subscales: core symptoms, melanoma-specific symptoms, total symptom burden, total interference, one comprised of walking, general activity, working (WAW), and another consisting of relationships with others, enjoyment of life, and mood (REM). Data are considered evaluable if at least half of the items in each scale are answered. The MDASI has evidence of content and construct validity in patients with cancer as well as sensitivity to capture symptomatic changes (Cleeland, 2000). The MDASI is structured to allow additional patient-generated symptom items to be added, creating disease or treatment-specific MDASI

modules. Utilizing a panel of three experts in treating advanced melanoma with ICI therapy, items from the MDASI symptom library were reviewed and agreed upon for inclusion in the Modified MDASI (Appendix A).

The FACT-M (Appendix B) is a self-report 51-item questionnaire designed to measure four domains of HRQOL in participants with melanoma: physical, social, emotional, and functional well-being. There is evidence of content validity and sensitivity in participants with melanoma (Cormier et al., 2005). Cormier et al. (2008) found the internal consistency and test-retest reliability (r) of the melanoma subscale (Cronbach α = .85, r = .81) and the total FACT-melanoma (α = .95, r = .90) which are evidence of the reliability and validity of the instrument (Carmines & Zeller, 1979). The FACT-M is derived from the Functional Assessment of Cancer Therapy- General (FACT-G) and asks about the experience in the past seven days, are rated 0 'not at all' to 4 'very much' with a total score of 0-172, and a higher score indicates better quality of life. The 27 items of the FACT-G are divided into four domains, Physical Well-Being (PWB, 7-items), Social and family Well-Being (SWB, 7-items), Emotional Well-Being (EWB, 6-items), and (Functional Well-Being, 7-items). The remaining items are split between the Melanoma Subscale (MS, 16-items) and the Melanoma Surgery Scale (MSS, 8-items). The FACIT scoring guideline was used for scoring the FACT-M, including reverse scoring as appropriate and handling missing data (FACIT, 2022).

Review of systems (ROS) data was obtained from notes documented in the EHR by the provider for the treatment clearance visit on the same day the PRO instruments were completed. Each symptom report was captured and counted for the total number of symptoms reported by the provider. The total number of symptoms reported on the Modified MDASI was counted and compared to the number of symptoms documented by the provider to obtain a degree of matching. Results were entered as 1 = complete match of symptoms reported in ROS and PRO instrument, 2 = not a match, less than three items reported on ROS that were not reported in PRO instrument, 3 = not a match, three or more symptoms reported in ROS that were not reported in PRO instrument, 4 = not a match, less than three symptoms reported in PRO instrument that were not reported in ROS or a 5 = not a match, three or more symptoms reported in PRO instrument that were not reported in ROS.

Statistical Analysis

Descriptive statistics were used to describe symptom burden, grade of therapy-related toxicities, and symptom-related interference, the symptoms rereported by the participants on the PRO instruments, and those documented by the clinicians (advanced practice provider or physician) in the EHR. Cohen's effect size and *t*-tests were used to determine differences between the two groups. ANOVA was used to assess the difference in means of the characteristics with three or more categories since the normal distribution assumption was met.

Results

Sample

Table 1 presents the participant characteristics of the entire sample (n=60). Participants had a median age of 61.4 (range 19-82); the majority were male (n = 34, 57%), white (n = 55, 92%), non-Hispanic (n = 57, 95%), married (n = 48, 80%), and employed full time (n=29, 48%), college graduate (n = 19, 32%), on single-agent therapy with nivolumab or pembrolizumab (n = 29, 48%), had AJCC stage IV (n = 35, 58%)and were treated in the metastatic setting (n = 35, 58%). All 60 participants had a documented Eastern Cooperative Oncology Group (ECOG) status of 0 or 1. The mean score for each item on the Modified MDASI is available in Table 2, ranking each item by mean severity and providing participants who rated an item > 4 for moderate severity and those rated >7 for high severity. Item severity is listed in rank order by mean and total scores for each subscale of the FACT-M (Table 3). To highlight those with a more significant impact of symptoms, we presented the participant's scores lower than 50% of the subscales max range.

Modified MDASI

Sixty participants completed the Modified MDASI, the Cronbach's α = .94, indicating evidence of excellent reliability. Symptoms that were experienced by greater than 50% of participants were lack of energy (n = 43, 72%), fatigue (n = 42, 71%), feeling drowsy (n = 35, 60%), joint stiffness/soreness (n = 34, 57%), disturbed sleep (n = 33, 56%), dry mouth (n = 32, 53%), and itching (n = 30,

50%). More than 50% of participants reported interference in their general activity (n = 33, 55%) and work (n = 32, 53%). Rare symptoms included vomiting (n = 5, 8%) and problems with teeth and gums (n = 6, 10%)

An independent-samples *t*-test was conducted to determine whether there were differences in the scores of the Modified MDASI between males and females (Table 4.1), with no differences found. An independent-samples *t*-test was conducted to determine whether there were differences in Modified MDASI core, melanoma-specific, and total symptom scores based on being older or younger than the mean age of 61.4 (Table 4.2). Significant differences were found in the MDASI core symptom burden between those younger than 61.4 (M=2.01, SD=2.05) and older than 61.4 (M=1.33, SD=1.32), [$t(58)=1.546$, $p=.005$], Cohen's d of .399, the melanoma-specific symptom burden between younger than 61.4 (M=1.56, SD=1.61) and older than 61.4 (M=1.17, SD=1.31), [$t(58)=1.033$, $p=.035$], Cohen's d of .267, and in the total symptom burden between younger than 61.4 (M=1.74, SD=1.72) and older than 61.4 (M=1.23, SD=1.27), [$t(58)=1.286$, $p=.015$], Cohen's d of .332. As each of Cohen's d was less than .4, it indicates a small effect size for these findings.

An independent-samples *t*-test was conducted to determine whether there is a difference in the Modified MDASI scores based on whether symptoms were reported in the clinical review of symptoms or not (Table 4.3). While the results showed no significant difference in the MDASI core symptom burden, differences in total interference scores were found between those with symptoms (M=1.91,

SD=2.21) and those that did not report symptoms (M=.74, SD=1.16), [*t*(58)=1.772, *p* =.020], Cohen's d (.572), the WAW interference score between those with symptoms (M=2.04, SD=2.35) and those that did not report symptoms (M=.78, SD=1.30), [*t*(58)=1.780, *p* =.035], Cohen's d (.575), and REM interference score between those with symptoms (M=1.78, SD=2.24) and those that did not report symptoms (M=.69, SD=1.27), [*t*(58)= 1.610 *p* =.017], Cohen's d (.518). Each of Cohen's d was greater than .5, indicating a moderate effect size of these findings.

An independent-samples *t*-test was conducted to determine whether there were differences in the Modified MDASI scores based on an ECOG performance score of 0 or 1 (Table 4.4). The results showed only a significant difference in the MDASI total interference mean scores between those with an EOCG of 0 (M=1.28, SD=1.82) and an ECOG of 1 (M=2.29, SD=1.63), [*t*(58)= -2.446, *p* =.050]. The effect size is large, with a Cohen's d of -.701.

An independent-samples *t*-test was conducted to determine whether there is a difference in the Modified MDASI total symptom and total interference scores between those on ICI therapy for less than six months and those six months or longer (Table 4.5). The results indicate there is no significant difference in the total symptom score between those on therapy less than six months (M=1.58, SD=1.39) and those six months or longer (M=1.33, SD=1.721), [*t*(58) = .622, *p* = .555] or the total interference score between those on therapy less than six months (M=1.95, SD=2.19) and those six months or longer (M=1.25, SD=1.88),

[*t*(58) = 1.290, *p* = .141]. Consequently, we fail to reject the null hypothesis that there is no difference between the sample means based on the amount of time on ICI therapy.

The ANOVA was significant (F (2,57) = 3.981, *p* = .024) for the means of the melanoma symptoms on the Modified MDASI (Table 5). A post hoc Tukey HSD test indicated that the mean melanoma symptom score of the adjuvant group was significantly lower than that of the metastatic group (*p* = .03). However, there were no significant differences between the mean melanoma symptom score of the adjuvant group and neoadjuvant group (*p* = .166) or the metastatic group and neoadjuvant group (*p* =.861). The ANOVA was significant at the 0.05 level, F (2,57) = 3.981, *p* = .024 for the means of the total symptom burden score of the Modified MDASI. A post hoc Tukey HSD test indicated that the adjuvant group's mean total symptom burden score was significantly lower than that of the metastatic group (*p* = .037). However, there were no significant differences between the mean Melanoma symptom score of the adjuvant group and neoadjuvant group (*p* = 0.332) or the metastatic group and neoadjuvant group (*p* = 0.988).

Functional Assessment of Cancer Therapy- Melanoma

Sixty participants completed the FACT-M, with Cronbach’s α = .90, indicating evidence of reliability. There were 31 missing items. One question asks participants about their sex life, but they can check a box if they do not want to answer it, so 13 items were missing by choice. All 60 participant's data were

evaluable despite missing items because each subscale had more than 50% of items answered, so each score could be calculated. Symptoms present in greater than 50% of the participants are fatigue (n= 49, 82%), lack of energy (n= 46, 77%), some impact on their sleep (n=44, 73.3%), worry that the condition will get worse (n=38, 63%), feeling nervous (n= 32, 54%), feeling sad (n= 32, 54%), and worry about dying (n= 30, 51%).

An independent-samples *t*-test was conducted to determine whether there is a difference in the FACT-M scores between males and females (Table 4.1), but no differences were found. An independent-samples *t*-test was conducted to determine whether there is a difference in the FACT-M scores based on being older or younger than the mean age of 61.4 (Table 4.2). The results showed a significant difference in the EWB subscale score between those younger than 61.4 (M=17.45, SD=4.76) and those older than 61.4 (M=19.45, SD=3.60), [$t(58)= -1.847$, $p=.044$], Cohen's d (-.360) indicates the effect size is small.

An independent-samples *t*-test was conducted to determine a difference in the FACT-M scores between those that reported symptoms on their clinical review of systems and those that did not (Table 4.3), with no differences found. An independent-samples *t*-test was conducted to determine whether there is a difference in the FACT-M scores based on ECOG of 0 or 1 (Table 4.4). The results showed a significant difference in the PWB score between those with an ECOG of 0 (M=24.12, SD=4.64) and with an ECOG of 1 (M=18.41, SD=7.38), [$t(58)= 3.598$, $p= .002$], the Cohen's d was 1.03 indicating a large effect size in

this sample. An independent-samples *t*-test was conducted to determine whether there is a difference in the FACT-M scores between those on ICI therapy for less than six months or six months and longer (Table 4.5), with no differences found.

A one-way ANOVA was performed to evaluate the relationship between the type of ICI therapy and the mean scores of the PRO instruments. The means and standard deviations are presented in Table 6. The ANOVA was significant at the 0.05 level, F (2,54) = 3.186, p = 0.049 for the means of the Physical Well-Being (PWB) score. However, the post hoc Tukey HSD test indicated that there were no significant differences between the PWB score mean of those treated with single-agent ICI and combination ipilimumab + nivolumab (p =0.096) nor those treated with single-agent ICI and combination nivolumab + relatlimab (p= 0.127) or combination ipilimumab + nivolumab or combination nivolumab + relatlimab (p= 0.989). A one-way ANOVA was performed to evaluate the relationship between the timing of therapy, adjuvant, neoadjuvant or metastatic, and the mean scores of the PRO instruments with no significant differences found.

Satisfaction

The first nine participants were not asked about their satisfaction with the PROs as it was not thought to be included until a participant offered their opinion on the surveys they had just completed. The final 51 participants answered the question of satisfaction regarding the PROs. The majority of participants were satisfied with the survey (n=41, 80%). Of the 10 participants noting dissatisfaction

with the PROs, the majority (n=9, 90%) stated an issue with the timing of symptom capture within the past seven days or 24 hours. They all reported that their symptoms were present or at least more intense in the first or second week. Two participants were concerned about the symptoms assessed. One noted that the surgical questions on the FACT-M did not apply to their situation. Another participant recommended asking about the financial burden or the inconvenience of therapy, pharmacy delays, and other aspects of navigating the system and insurance. One suggested a separate section to compare a symptom now vs. baseline to give some context of burden. Another participant recommended using an instrument the caregiver would fill out to provide another perspective on the ICI impact on the functionality and mood of the patient.

Degree of Matching

The majority of participants (n = 46, 76%) reported three or more symptoms on either PRO instrument than the number documented in the clinician's ROS in the EHR. Of these, 40 (67%) reported three or more symptoms in the Modified MDASI and the FACT-M (Table 6). Four (6.7%) participants documented the same number of symptoms on the clinician ROS as they documented on the FACT-M (n= 1) or the Modified MDASI (n=3). However, they did not report the same symptoms on each PRO instrument (e.g., four symptoms on the FACT-M and seven on the Modified MDASI). We could not compare intensity or interference as none of the symptoms reported in the clinician ROS were graded with the CTCAE scale. We can infer that since clinicians assessed

all participants with an ECOG 0-1, minimal to no functional status impairment was observed during the visit. This is slightly different from the participants (n=7) that indicated moderate to severe inference by reporting a score > 7 on at least one of the Modified MDASI interference questions, or the participants (n=8) reported a subscale score of less than 50% on the PWB, SWB, FWB, and/or EWB of the FACT-M.

Discussion

Here we describe the quantitative results of a cross-sectional study that evaluated the symptom presence, burden, and interference of patients with advanced melanoma undergoing ICI therapy. It was found that patients had heterogeneous experiences, with some having a high burden of symptoms that significantly impacted their domains of HRQoL. In contrast, others had minimal burden with negligible impact on their HRQoL. In previous studies, the presence of any grade toxicities related to treatment varied between 68%-85.2%, and the rate of intense (grade 3-4) toxicities was 13.3%-55%, with fatigue as the most often reported symptom (Larkin et al., 2015; Robert et al., 2015; Tawbi et al., 2022; J. Weber et al., 2017; J. S. Weber et al., 2015). In this study, all participants experienced toxicities at some grade, and 23.7% reported severe symptoms (score >7) on the Modified MDASI. The most common symptoms reported in this study on the FACT-M and Modified MDASI were fatigue, sadness, nervousness, and worry about dying or the disease worsening. Distress was not reported in previous studies that led to FDA approval for the ICIs included in this study (Larkin et al., 2015; Robert et al., 2015; Tawbi et al., 2022;

J. Weber et al., 2017; J. S. Weber et al., 2015), despite each of them utilizing a PRO instrument that evaluated emotional burden. This may suggest clinicians are not capturing the full spectrum of toxicities participants endure with the current ROS evaluation methods and existing PRO measures. Distress has been studied in the general oncology population, and studies note a prevalence of emotional distress from 35% to 70% of patients (Bultz & Carlson, 2005) and recent studies report an impact on survival related to distress (Antoni et al., 2017; Vodermaier et al., 2017). Our findings support the need for further research in evaluating and managing emotional distress for patients across the oncology spectrum.

Scores on the FACT-M subscales among our sample were lower, indicating more interference, than in previous studies that included the FACT-M to evaluate participants with melanoma (Cormier et al., 2008; Lindqvist Bagge et al., 2021; Winstanley et al., 2013). This could be attributed to the fact that the studies by Cormier and Winstanley included Stage I participants in their evaluation. It is unclear whether these participants were undergoing systemic therapy when the instrument was completed. Conversely, the mean FACT-G scores in the current study (84.6) were slightly higher than those from a study by Shuk et al. (2016) which evaluated participants on ipilimumab alone at baseline (76.8), week 9 (79.4) and 12 weeks later without progression (82.6) and those with progression (79.9). To account for the difference is difficult as the samples appear similar aside from the therapeutic agent used. The participants in the study used ipilimumab in combination with nivolumab (30%); none utilized it as a

single agent. As the Modified MDASI has not been utilized in any prior research, there are no outcomes to compare for the patient with advanced melanoma.

It has been well documented that concordance between PRO data and clinician-based assessment with Common Terminology Criteria for Adverse Events (CTCAE) is low to moderate (Atkinson et al., 2016; Basch et al., 2009). Clinicians and patients do not always communicate well regarding the patient's experience of symptoms, and clinicians tend to underestimate or at least under-document the frequency, severity, and impact of symptoms on the patient (Basch et al., 2009; Laugsand et al., 2010; Xiao et al., 2013). Our findings are consistent with this as most participants (n = 46) reported more symptoms in the PRO instruments than those documented in the clinicians' ROS.

Current literature shows patients are willing to answer PRO instruments (Albaba et al., 2019; Atkinson et al., 2019; Whisenant et al., 2021). Thus, using PRO measures can improve well-being and quality of life, and including PRO data can improve clinical outcomes and survival (Basch et al., 2017; Denis et al., 2019). Developing a PRO measure specific to patients with melanoma receiving ICIs requires additional research. Participants did not always report the same symptoms in the FACT-M as in the Modified MDASI. As evidenced by the evaluation of matching the ROS to the PROs, the one participant that matched symptoms on the FACT-M to those reported was not one of the three participants that noted the same symptoms on the Modified MDASI as in their ROS. A larger sample will be essential to find the most appropriate wording and confirm which

symptoms need to be assessed on a PRO for patients with melanoma receiving ICIs.

Limitations

Limitations of this sample include the modest number of 60 participants, 55 (92%) of whom were white and the majority educated with at least some college (n= 54, 90%). In addition, our study was conducted at a single academic center in a large metropolitan city and may not be representative of the entire melanoma population. Bias is possible, especially when a study is not randomized. To minimize bias in this study, the PI did not complete any clinical assessments and ROS of the participants on the day they consented and completed the PRO instruments. As this was an exploratory study and multiple means test evaluated, one must be aware of the Type 1 error and not conclude any causality in relationships.

Conclusion

The findings of this study expose areas requiring further research. Considering the heterogeneity of the participant responses within the two PRO instruments about symptom burden and interference, additional work is needed to create melanoma ICI-specific PRO measures. This will allow researchers to capture longitudinal data clinically and in future trials to improve monitoring, assessment of interventions, and patient outcomes. Due to the variety in HRQoL total and subscale scores, there is a need to evaluate further the patient experience and ask which HRQoL measures are meaningful to the patients and if

the current PRO measures are adequate. More research is needed to address the stark difference between the symptom presence and burden captured with the PROs compared to those reported to the clinician at the visit via ROS. Further research is needed to increase the awareness of the benefit and subsequent use of PROs for symptom monitoring outside of clinical trials and facilitating improved symptom discussions between clinicians and patients.

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Table 1

Demographic and clinical characteristics for study participants (n=60)

Characteristic	N (%)
Age	
Median (range)	61.4 (19-82)
Sex	
Male	34 (57)
Female	26 (43)
ECOG Performance	
0	43 (72)
1	17 (18)
Race	
White	55 (91.7)
Black	1 (1.7)
Asian	2 (3.3)
Hispanic	2 (3.3)
Ethnicity	
Hispanic	3 (5)
Non-Hispanic	57 (95)
Marital Status	
Married	48 (80)
Single	5 (8.3)
Divorced	3 (5)
Significant Other	3 (5)
Widowed	1 (1.7)
Education	
9th grade	1 (1.7)
High School diploma/graduate	5 (8.3)
Some college	17 (28.3)
College Graduate	19 (31.7)
Graduate/Professional Training	17 (28.3)
Employment Status	
Employed full-time	29 (48.3)
Retired	20 (33.3)
Employed part-time	5 (8.3)
Homemaker	3 (5)
Unemployed	2 (3.3)
Disabled due to illness	1 (1.7)
Therapy	
Nivolumab	18 (28)
Ipilimumab + Nivolumab	17 (30)
Pembrolizumab	11 (18)
Nivolumab + relatlimab	11 (18)
Blinded Clinical trial with Nivo vs Nivo+Rela	3 (5)

Table 1

Continued

Characteristic	N (%)
Timing of therapy	
Adjuvant	21 (35)
Neoadjuvant	4 (7)
Metastatic	35 (58)
Disease Stage	
Stage II	5 (8)
Stage III	20 (33)
Stage IV	35 (58)
Clinician Review of Symptoms	
Symptoms present	46 (77)
Symptoms not present	14 (23)

Table 2

MD Anderson Symptom Inventory item prevalence and severity in rank order by mean severity

Items		N	Mean (SD)	Median (min, max)	# rated > 0 N (%)	# rated 4-10 N (%)	# rated 7- 10
Core symptom items	Fatigue	59	3.25 (3.08)	3 (0, 10)	42 (71)	25 (42)	13 (22)
	Disturbed sleep	59	2.85 (3.36)	2 (0, 10)	33 (56)	22 (37)	14 (24)
	Dry mouth	60	2.22 (2.92)	1 (0, 10)	32 (53)	16 (27)	9 (15)
	Feeling drowsy	58	2.22 (2.82)	1 (0, 9)	35 (60)	16 (28)	8 (14)
	Pain	60	1.97 (2.87)	0 (0, 10)	28 (47)	15 (25)	7 (12)
	Being distressed	60	1.92 (2.61)	0 (0, 10)	29 (48)	14 (23)	6 (10)
	Remembering things	60	1.53 (2.16)	0 (0, 7)	28 (47)	12 (20)	1 (2)
	Lack of appetite	60	1.32 (2.54)	0 (0, 10)	22 (37)	7 (12)	6 (10)
	Feeling sad	60	1.20 (2.02)	0 (0, 9)	25 (42)	8 (13)	2 (3)
	Shortness of breath	60	1.07 (2.07)	0 (0, 8)	18 (30)	9 (15)	2 (3)
	Numbness or tingling	60	1.05 (2.18)	0 (0, 10)	19 (32)	5 (8)	3 (5)
	Nausea	60	.82 (1.81)	0 (0, 8)	16 (27)	4 (7)	3 (5)
	Vomiting	60	.30 (1.44)	0 (0, 10)	5 (8)	2 (3)	1 (2)
Melanoma specific symptom items	Lack of energy	60	3.17 (3.11)	2 (0, 10)	43 (72)	23 (38)	12 (20)
	Joint stiffness/soreness	60	2.10 (2.60)	1 (0, 9)	34 (57)	15 (25)	7 (12)
	Malaise/not feeling well	60	1.95 (2.76)	0 (0, 8)	27 (45)	16 (27)	8 (13)
	Itching	60	1.92 (2.72)	0.5 (0, 10)	30 (50)	13 (22)	5 (8)
	Rash or skin changes	60	1.87 (2.97)	0 (0, 10)	27 (45)	12 (20)	8 (13)
	Irritability	60	1.80 (2.64)	0 (0, 10)	29 (48)	12 (20)	5 (8)
	Skin problems	59	1.69 (2.93)	0 (0, 10)	23 (39)	10 (17)	9 (15)
	Muscle weakness	60	1.58 (2.49)	0 (0, 9)	25 (42)	12 (20)	3 (5)
	Muscle soreness/cramping	60	1.50 (2.38)	0 (0, 9)	26 (43)	11 (18)	3 (5)

Table 2

Continued

Items		N	Mean (SD)	Median (min, max)	# rated > 0 N (%)	# rated 4-10 N (%)	# rated 7- 10
Melanoma specific symptom	Weakness in arms or legs	59	1.49 (2.47)	0 (0, 9)	23 (39)	9 (15)	5 (8.5)
	Problems with concentrating	59	1.39 (1.96)	0 (0, 8)	28 (48)	9 (15)	1 (1.7)
	Problems with feeling cold	60	1.37 (2.25)	0 (0, 9)	24 (40)	10 (17)	3 (5)
	Eye problems	60	1.25 (2.10)	0 (0, 10)	24 (40)	9 (15)	1 (1.7)
	Headache	60	1.25 (2.31)	0 (0, 10)	22 (37)	8 (13)	3 (5)
	Problems with feeling hot	60	.83 (1.59)	0 (0, 6)	17 (28)	6 (10)	0 (0)
	Fever or chills	60	.73 (2.10)	0 (0, 9)	10 (17)	5 (8.3)	3 (5)
	Issues with balance	60	.73 (1.48)	0 (0, 9)	20 (33)	2 (3.3)	1 (1.7)
	Dizziness	59	.66 (1.46)	0 (0, 8)	17 (29)	2 (3.4)	1 (1.7)
	Pain in the abdomen	60	.65 (1.39)	0 (0, 7)	16 (27)	3 (5)	1 (1.7)
	Mouth/throat sores	60	.43 (1.41)	0 (0, 8)	8 (13)	2 (3.3)	1 (1.7)
	Problem with the teeth or gums	60	.23 (.77)	0 (0, 4)	6 (10)	1 (1.7)	0 (0)
Interference	Mood	60	2.08 (2.53)	1 (0, 8)	27 (45)	12 (20)	3 (5)
	Work	60	1.70 (2.41)	0 (0, 7)	32 (53)	16 (27)	7 (12)
	Relations with others	60	2.17 (2.76)	1 (0, 9)	24 (40)	10 (17)	4 (6.7)
	Walking	60	1.35 (2.22)	0 (0, 8)	17 (28)	8 (13)	4 (6.7)
	Enjoyment of Life	60	1.10 (2.19)	0 (0, 8)	23 (38)	13 (95)	4 (6.7)
	General activity	60	1.63 (2.54)	0 (0, 9)	33 (55)	16 (95)	6 (10)
Composite scores							
	Core	60	1.66 (2.54)	1.08 (0, 6.3)	55 (92)	6 (10)	0 (0)
	Melanoma	60	1.36 (1.46)	0.95 (0, 5.1)	57 (95)	4 (7)	0 (0)
	Total symptom	60	1.48 (1.52)	0.87 (0, 5.6)	57 (95)	6 (10)	0 (0)
	Total Interference	60	1.67 (2.08)	0.83 (0, 7)	42 (70)	8 (13)	2 (3.3)
	WAW	60	1.78 (2.23)	0.83 (0, 8)	38 (63)	9 (15)	4 (6.7)
	REM	60	1.56 (2.12)	.33 (0, 7)	32 (53)	11 (18)	1 (1.7)

WAW= **W**alking, General **A**ctivity, **W**orking; REM = **R**elationships with others, **E**njoyment of life, **M**ood

Table 3

Functional Assessment of Cancer Therapy – Melanoma item severity in rank order by mean with subscale scores

Item	N	Mean (SD)	Median (min, max)	# rated > 0 N (%)	# rated 3-4 N (%)
Good Range of Motion [1]	60	2.85 (1.67)	4 (0, 4)	24 (40)	15 (25)
Good Appetite [1]	60	2.82 (1.27)	3 (0, 4)	36 (60)	11 (18.3)
Sleeping well [1]	60	2.63 (1.15)	3 (0, 4)	44 (73.3)	10 (16.7)
Fatigue	60	1.45 (1.02)	1 (0, 4)	49 (81.7)	10 (16.7)
Lack of energy	60	1.45 (1.21)	1 (0, 4)	46 (76.7)	10 (16.7)
Worry my condition will get worse	60	1.37 (1.35)	1 (0, 4)	38 (63.3)	15 (25.0)
Aches and pains in bones	60	0.98 (1.30)	0 (0, 4)	29 (48.3)	7 (11.7)
Worry about dying	59	0.93 (1.20)	1 (0, 4)	30 (50.8)	7 (11.7)
Feel nervous	59	0.88 (1.00)	1 (1, 4)	32 (54.2)	6 (10)
Pain	59	0.88 (1.29)	0 (0, 4)	25 (42.4)	10 (16.7)
Feel sad	59	0.86 (0.99)	1 (0, 4)	32 (54.2)	4 (6.7)
Difficulty remembering /concentrating	60	0.72 (1.01)	0 (0, 4)	26 (43.3)	5 (8.3)
Headaches	60	0.70 (0.93)	0 (0, 4)	28 (46.7)	3 (5)
Skin changes	60	0.70 (1.06)	0 (0, 4)	22 (36.7)	5 (8.3)
Numbness at surgical site	60	0.68 (1.13)	0 (0, 4)	20 (33.3)	6 (10)
Overwhelmed by condition	59	0.63 (0.89)	0 (0, 3)	24 (40.7)	3 (5)
Pain at surgical site	60	0.60 (0.94)	0 (0, 4)	23 (38.3)	4 (6.7)
Feel ill	60	0.52 (1.00)	0 (0, 4)	16 (98.3)	5 (8.3)

Note. (1)= reverse scored

Table 3

Continued

Item	N	Mean (SD)	Median (min, max)	# rated > 0 N (%)	# rated 3-4 N (%)
Shortness of Breath	59	0.37 (0.76)	0 (0, 3)	14 (23.7)	2 (3.3)
Nausea	59	0.36 (0.69)	0 (1, 4)	17 (28.3)	2 (3.3)
Worry about appearance of surgical scars	59	0.36 (0.76)	0 (0, 3)	14 (23.3)	2 (3.3)
Fevers	60	0.35 (0.86)	0 (0, 4)	11 (18.3)	3 (5)
Swelling/cramps stomach	60	0.30 (0.70)	0 (0, 3)	11 (18.3)	1 (1.7)
Swelling at melanoma site	60	0.18 (0.54)	0 (1, 4)	8 (13.3)	0 (0)
Blood in stool	60	0.02 (0.13)	0 (0, 1)	1 (1.7)	0 (0)

	FACT-M Subscales (n=60)	Score Range	Score-Mean (SD)	Median (min, max)	Scores <50% range max
	Physical well-being (PWB)	0-28	22.5 (6.07)	25 (6, 28)	8 (13.3)
	Social/Family well-being (SWB)	0-28	22.5 (5.18)	24 (10, 28)	6 (10)
	Emotional well-being (EWB)	0-24	18.5 (4.28)	19 (8, 24)	7 (11.7)
	Functional well-being (FWB)	0-28	21.2 (5.53)	21.5 (7, 28)	6 (10)
	Melanoma Subscale (MS)	0-64	53.5 (7.76)	56 (36, 63)	0 (0)
	Melanoma surgery subscale (MSS)	0-32	29.0 (3.24)	29.5 (18, 32)	0 (0)
	Summary Composite Scales (n=60)	**Score Range**	**Score-Mean (SD)**	**Median (min, max)**	**Scores <50% max**
	FACT-M TOI FACT-G FACT-M Total	0-120 0-108 0-172	97.1 (17.49) 84.6 (15.87) 138.1 (22.49)	103 (51, 119) 88 (41, 108) 144 (77, 169)	2 (3.4) 1 (1.7) 1 (1.7)

Note. FACT-M TOI= Functional Assessment of Cancer Therapy – Melanoma Trial Outcome Index (sum of PWB + FWB + MS); FACT-G= Functional Assessment of Cancer Therapy- General and is a (sum of PWB + SWB + EWB + FWB); FACT-M Total is a (sum of PWB + SWB + EWB + FWB + MS)

Table 4.1

Description of the tests of mean differences in subscale scores for gender

Measure	**Female (n=26)**		**Male (n=34)**		(*df*=2,58)		*Mean difference*
	M	SD	Mean	SD	*t*	*p*	
MDASI Core symptom score	1.44	1.55	1.83	1.86	.858	.301	-.388
Melanoma-specific score	1.25	1.44	1.45	1.49	.535	.536	-.205
MDASI Total symptom score	1.32	1.41	1.60	1.61	.689	.380	-.273
MDASI Interference score	1.83	2.19	1.55	2.02	-.500	.296	.273
MDASI WAW	1.99	2.40	1.63	2.11	.617	.285	.360
MDAS REM	1.67	2.14	1.48	2.13	.335	.552	.186
FACTM-PWB	22.15	6.57	22.76	5.74	.384	.708	-.611
FACTM-SWB	22.50	5.32	22.50	5.16	.000	.386	.000
FACTM- EWB	17.62	4.69	19.15	3.89	1.383	.150	-1.532
FACTM-FWB	21.35	5.73	21.00	5.45	-.239	.384	.346
FACTM-MS	53.12	7.59	53.76	7.99	.319	.717	-.649
FACTM-FACTG score	83.62	15.79	85.41	16.13	-.431	.704	-1.796
FACTM-Total	136.73	22.22	139.18	22.98	.414	.729	-2.446

MDASI= MD Anderson Symptom Inventory, WAW= **w**alking, general **a**ctivity, **w**ork, REM= **r**elationships with others, **e**njoyment of life, **m**ood , FACT= Functional Assessment of Cancer Therapy, PWB= Physical Well-being, SWB= Social Well-being, EWB = Emotional Well-being, FWB= Functional Well-being, MS= Melanoma Specific, G= General

*$p < .05$

Table 4.2

Description of the tests of mean differences in subscale scores based on median age of 61.4

Measure	**Age < median (n=29)**		**Age ≥ median (n=31)**		(*df*=2,58)		*Mean difference*
	Mean	SD	M	SD	*t*	*p*	
MDASI Core symptom score	2.01	2.05	1.33	1.32	1.546	.005*	.682
Melanoma-specific score	1.56	1.61	1.17	1.31	1.033	.035*	.390
MDASI Total symptom score	1.74	1.72	1.23	1.27	1.286	.015*	.501
MDASI Interference score	1.76	2.20	1.59	2.00	.329	.253	.178
MDASI WAW	1.71	2.17	1.85	2.32	-.236	.896	-.137
MDASI REM	1.82	2.36	1.32	1.87	.900	.113	.494
FACTM-PWB	22.24	5.80	22.74	6.40	-.317	.694	-.501
FACTM-SWB	21.76	5.15	23.19	5.20	-1.073	.899	-1.435
FACTM- EWB	17.45	4.76	19.45	3.60	-1.847	.044*	-2.003
FACTM-FWB	19.83	5.86	22.39	4.97	-1.828	.500	-2.560
FACTM-MS	52.83	8.29	54.10	7.30	-.630	.360	-1.269
FACTM-FACTG score	81.28	16.63	87.77	14.71	-1.606	.477	-6.498
FACTM-Total	134.10	23.82	141.87	20.86	-1.346	.400	-7.768

Note. MDASI= MD Anderson Symptom Inventory, WAW= **w**alking, general **a**ctivity, **w**ork, REM= **r**elationships with others, **e**njoyment of life, **m**ood , FACT= Functional Assessment of Cancer Therapy, PWB= Physical Well-being, SWB= Social Well-being, EWB = Emotional Well-being, FWB= Functional Well-being, MS= Melanoma Specific, G= General

*$p < .05$

Table 4.3

Description of the tests of mean differences in subscale scores of symptom presence on review of systems

Measure	**Symptoms present on Review of Systems (n=48)**		**Symptoms not present on Review of Systems (n=12)**		(*df*=2,58)		*Mean difference*
	Mean	SD	Mean	SD	*t*	*p*	
MDASI Core symptom score	1.82	1.69	1.04	1.82	1.399	.645	.774
Melanoma-specific score	1.55	1.50	.61	1.06	2.040	.056	.938
MDASI Total symptom score	1.65	1.52	.78	1.35	1.825	.233	.876
MDASI Interference score	1.91	2.21	.74	1.16	1.772	.020*	1.170
MDASI WAW	2.04	2.35	.78	1.30	1.780	.035*	1.257
MDASI REM	1.78	2.24	.69	1.27	1.610	.017*	1.083
FACTM-PWB	21.83	6.17	25.17	5.01	-1.730	.276	-3.333
FACTM-SWB	22.50	4.96	22.50	6.23	0.000	.462	.000
FACTM- EWB	18.04	4.27	20.25	4.03	-1.619	.478	-2.208
FACTM-FWB	20.83	5.26	22.42	6.60	-.886	.131	-1.583
FACTM-MS	52.48	7.69	57.50	6.95	-2.060	.290	-5.021
FACTM-FACTG score	83.21	15.16	90.33	18.02	-1.402	.264	-7.125
FACTM-Total	135.69	21.55	147.83	24.50	-1.700	.458	-12.146

Note. MDASI= MD Anderson Symptom Inventory, WAW= **w**alking, general **a**ctivity, **w**ork, REM= **r**elationships with others, **e**njoyment of life, **m**ood , FACT= Functional Assessment of Cancer Therapy, PWB= Physical Well-being, SWB= Social Well-being, EWB = Emotional Well-being, FWB= Functional Well-being, MS= Melanoma Specific, G= General

*$p < .05$

Table 4.4

Description of the Tests of mean differences in subscale scores of ECOG 0 vs. 1

Measure	**ECOG 0 (n=43)**		**ECOG 1 (n=17)**		(*df*=2,58)		*Mean difference*
	Mean	SD	Mean	SD	*t*	*p*	
MDASI Core symptom score	1.29	1.53	2.60	1.88	-2.816	.102	-1.320
Melanoma-specific score	1.07	1.30	2.10	1.63	-2.567	.075	-1.028
MDASI Total symptom score	1.15	1.36	2.29	1.63	-2.763	.217	-1.138
MDASI Interference score	1.28	1.82	2.68	2.40	-2.446	.050*	-1.401
MDASI WAW	1.28	1.87	3.06	2.58	-2.970	.099	-1.780
MDASI REM	1.27	1.92	2.29	2.45	-1.713	.051	-1.023
FACTM-PWB	24.12	4.64	18.41	7.38	3.598	.002*	5.705
FACTM-SWB	22.07	5.22	23.59	5.09	-1.023	.589	-1.518
FACTM-EWB	18.98	4.32	17.24	4.04	1.431	.930	1.741
FACTM-FWB	21.28	5.51	20.82	5.71	.285	.866	.456
FACTM-MS	54.95	7.23	49.76	8.00	2.430	.613	5.189
FACTM-FACTG score	86.44	15.49	80.06	16.37	1.416	.685	6.383
FACTM-Total	141.40	21.61	129.82	23.20	1.831	.542	11.572

Note. MDASI= MD Anderson Symptom Inventory, WAW= **w**alking, general **a**ctivity, **w**ork, REM= **r**elationships with others, **e**njoyment of life, **m**ood , FACT= Functional Assessment of Cancer Therapy, PWB= Physical Well-being, SWB= Social Well-being, EWB = Emotional Well-being, FWB= Functional Well-being, MS= Melanoma Specific, G= General

*$p < .05$

Table 4.5

Description of the tests of mean differences in subscales cores for time in months on current therapy

Measure	**< 6 months (n=36)**		**≥ 6 months (n=24)**		(*df*=2,58)		*Mean difference*
	Mean	SD	Mean	SD	*t*	*p*	
MDASI Core symptom score	1.79	1.58	1.47	1.94	.703	.679	.322
Melanoma-specific score	1.44	1.36	1.24	1.63	.535	.606	.207
MDASI Total symptom score	1.58	1.39	1.33	1.72	.622	.555	.250
MDASI Interference score	1.95	2.19	1.25	1.88	1.290	.141	.704
MDASI WAW	2.05	2.32	1.39	2.06	1.123	.215	.657
MDASI REM	1.86	2.28	1.11	1.80	1.353	.081	.750
FACTM-PWB	21.64	6.36	23.79	5.48	-1.356	.336	-2.153
FACTM-SWB	22.47	5.19	22.54	5.28	-.050	.935	-.069
FACTM-EWB	18.11	4.37	19.04	4.18	-.822	.920	-.931
FACTM-FWB	21.14	5.72	21.17	5.34	-.019	.698	-.028
FACTM-MS	52.86	7.78	54.42	7.79	-.758	.686	-1.556
FACTM-FACTG score	83.36	16.66	86.54	14.76	-.758	.290	-3.181
FACTM-Total	136.22	23.43	140.96	21.27	-.797	.285	-4.736

Note. MDASI= MD Anderson Symptom Inventory, WAW= **w**alking, general **a**ctivity, **w**ork, REM= **r**elationships with others, **e**njoyment of life, **m**ood , FACT= Functional Assessment of Cancer Therapy, PWB= Physical Well-being, SWB= Social Well-being, EWB = Emotional Well-being, FWB= Functional Well-being, MS= Melanoma Specific, G= General

*$p < .05$

Table 5

Tests of mean differences in subscale scores for modified MD Anderson Symptom Inventory and Functional Assessment of Cancer Therapy - Melanoma for timing of therapy, treatment type, and AJCC stage

Subscale score	**Clinical variable**					
	Timing of therapy (n=60) *df*=2,57 (adjuvant = 20, metastatic = 36, neoadjuvant = 4)		**Treatment Type (n=57^) *df*=2,54 (single = 29, combo I + N = 17, combo R + N = 11)**		**AJCC Stage (n=60) *df*=2,57 (II = 5, III = 20, IV = 35)**	
MD Anderson Symptom Inventory	**F**	***p***	**F**	***p***	**F**	***p***
Core Symptoms	2.434	.097	.664	.519	2.361	.103
Melanoma-specific symptoms	3.981	.024*	1.211	.306	2.547	.087
Total symptoms	3.397	.040*	.936	.399	2.646	.080
Total Interference	1.284	.285	1.288	.284	1.168	.318
WAW	1.604	.210	2.149	.126	1.337	.271
REM	.874	.423	.497	.611	.869	.425
FACT-melanoma						
Physical WB	2.783	.070	2.420	.099	2.785	.070
Social WB	1.926	.155	2.167	.124	1.644	.202
Emotional WB	.647	.528	2.404	.100	.202	.818
Functional WB	.659	.521	3.186	.049*	.037	.963
Melanoma Specific	1.192	.311	.781	.463	1.028	.364
FACT-General	.096	.909	1.434	.247	.018	.982
TOTAL	.107	.899	.917	.406	.158	.854

Note. (^)= 3 patients were on a blinded adjuvant clinical trial with nivolumab vs. relatlimab + nivolumab; MDASI= MD Anderson Symptom Inventory; WAW= **w**alking, general **a**ctivity, **w**ork; REM= **r**elationships with others, **e**njoyment of life, **m**ood; FACT= Functional Assessment of Cancer Therapy, PWB= Physical Well-being, SWB= Social Well-being; EWB = Emotional Well-being; FWB= Functional Well-being; MS= Melanoma Specific; G= General

*$p < .05$

Table 6

Degree of matching between symptoms reported in the review of symptoms and those on the modified MD Anderson Symptom Inventory and Functional Assessment of Cancer Therapy - Melanoma

Scale and degree definition		All study participants N=60 (%)
MD Anderson Symptom Inventory		
	1= Complete match	3 (5)
	2= more on ROS than instrument but < 3	2 (3)
	3= more on ROS than instrument ≥ 3	0 (0)
	4= more on the instrument than ROS but < 3	9 (15)
	5= more on the instrument than ROS ≥ 3	46 (77)
Functional Assessment of Cancer Therapy-Melanoma		
	1= Complete match	1 (2)
	2= more on ROS than instrument but < 3	1 (2)
	3= more on ROS than instrument ≥ 3	0 (0)
	4= more on the instrument than ROS but < 3	12 (20)
	5= more on the instrument than ROS ≥ 3	46 (77)

Note. ROS= review of symptoms

Appendix A

Institutional Approvals

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Office of Human Subject Protection
7007 Bertner Avenue - Unit 1637
Houston, Texas 77030
Mainline: 713-792-6477 (2-6477)

APPROVAL

August 18, 2022

Xin Shelley Wang
Symptom Research CAO

On 8/18/2022, the IRB reviewed the following protocol:

IRB ID	BS99-094 MOD022
Type of Review:	Modification / Update
Level of Review:	Expedited
Review Category:	None (5) Data, documents, records, or specimens
Home IRB:	IRB 4
Title:	MEASURING THE SYMPTOM DISTRESS OF CANCER PATIENTS: DEVELOPMENT OF A NEW ASSESSMENT SYSTEM
Funding:	Name: Merck & Co.; Name: Bayer HealthCare AG; Name: Bristol-Myers Squibb; Name: Eli Lilly
IND, IDE or HDE:	None
Documents Reviewed:	• FACIT license for Individual Investigators - 30Jun2020_encrypted_.pdf, Category: Other; • FACT-M_ENG_Final_Ver4_16Nov07.pdf, Category: Other; • MDASI Modified.docx, Category: Other;

You will conduct this Human Research in accordance with requirements in HRP-103 - INVESTIGATOR MANUAL.

Sincerely,

Michelle Linares
cc:
FWA #: 00000363
OHRP IRB Registration Number: IRB 4 IRB00005015

UTHealth
The University of Texas
Health Science Center at Houston

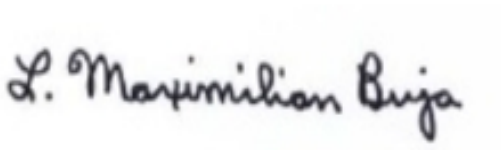
Committee for the Protection of Human Subjects
6410 Fannin Street, Suite 1100
Houston, Texas 77030

Meagan Whisenant
UT-H - SN - Nursing Research

May 28,
2020

NOTICE OF PERMISSION TO RELY ON THE UNIVERSITY OF TEXAS MD ANDERSON CANCER IRB

HSC-SN-20-0579 - Measuring the symptom distress of cancer patients: development of a new assessment system

CHAIRPERSON: L. Maximilian Buja,, MD 

PROVISIONS: This permission relates to the research to be conducted under the above referenced title.

CPHS has reviewed the above submission and determined that it meets the criteria for being reviewed by the University of Texas MD Anderson Cancer Center IRB. Please submit an application to the University of Texas MD Anderson Cancer Center IRB via their electronic system and await written approval.

Research participants must sign authorization for release of medical records unless such authorization is waived by the University of Texas MD Anderson Cancer Center IRB or UT Houston CPHS.

The research should not be initiated until all necessary institutional approvals and signatures have been obtained including but not limited to a fully executed clinical trial agreement.

Appendix B

Consent Form

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Measuring the Symptom Distress of Cancer Patients: Development of a New Assessment System
BS99-094

Subtitle: MD Anderson Consent - MDASI Validation

Study Chair: Xin Shelley Wang

STONE, COLTON	2662782
Participant's Name	Medical Record Number

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

STUDY SUMMARY

The purpose of this study is to try to learn more about common symptoms that may occur in patients due to cancer and its treatment. We also want to learn more about the impact of symptoms on your daily life. Another goal is to learn how to better measure symptoms systematically when caring for patients.

This is an investigational study.

Future patients may benefit from what is learned about symptom evaluation. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including potential expenses and time commitment. You may choose not to take part in this

study because of the time commitment or because some of the questions may be sensitive.

You can read a list of potential risks below in the Possible Risks section of this consent.

There is no cost to you for taking part in this study.

Your participation in this study is expected to last for as long as the study research coordinator explains to you that it will last. It could be that you will be asked to complete a single interview or assessment, or you may be asked to complete assessments over a specific period of time.

You may choose not to take part in this study.

1. STUDY DETAILS

Up to 8,500 participants will participate in this multicenter study. Up to 8,000 will be enrolled at MD Anderson.

In order to identify symptoms that are specific to a particular cancer, cancer stage, or treatment, you may be asked to take part in an interview. During this interview, the research staff may ask you questions about symptoms you have had since you were diagnosed, including during treatment, and how you are feeling now. The interviewer may ask follow-up questions to get more complete information about your symptoms. Interviews are digitally recorded and then transcribed (written out in text) later. Completing the interview along with other surveys takes about 15-45 minutes total, depending on the length of your interview.

You may be asked to complete a symptom survey using paper and pencil, a secure electronic method, or the telephone. You may be asked to complete additional surveys about how the disease is affecting you. If you are asked to use the phone method, you may receive a personal call, or we may use an automated interactive voice response (IVR) telephone system to contact you. The research study staff will ask you for a convenient time to call. How often you will be asked to complete the surveys depends on the type of cancer you have and the treatment you are receiving. Completing these surveys takes 10-25 minutes. The research study staff will give you more information about the surveys you will be asked to complete and the number of times you will be asked to complete the surveys over the course of the study.

Information about your symptoms in this study is collected for research purposes only. If you are experiencing severe or troublesome symptoms, you should report them to your doctor or nurse as well as rating them on the symptom assessment questionnaire. If the data collector notices that you have rated a symptom as severe, the data collector will ask you if your doctor or nurse is aware of the symptom or if you intend to report the symptom to your doctor or nurse. If you have not or do not intend

to report the symptom, the data collector will let you know that he or she will report the symptom to your doctor or nurse.

You may be asked to provide some personal information, such as employment or education.

2. POSSIBLE RISKS

Questionnaires may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns about completing the questionnaire, you are encouraged to contact your doctor or the study chair.

This study may involve unpredictable risks to the participants.

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson, Bristol-Myers Squibb Company, Bayer HealthCare Pharmaceuticals, Merck & Co., Inc., or Eli Lilly and Company for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Unless otherwise stated in this consent form, all of the costs linked with this study, which are not covered by other payers (health maintenance organization [HMO], health insurance company, etc.), will be your responsibility.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Xin Shelley Wang, at 713-745-3470) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you

withdraw from this study, you can still choose to be treated at MD Anderson.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, Bristol-Myers Squibb Company, Bayer HealthCare Pharmaceuticals, Merck & Co., Inc., Eli Lilly and Company, or the IRB of MD Anderson.

7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study, and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

8. MD Anderson may benefit from your participation and/or what is learned in this study.

9. This study is sponsored and/or supported by: Bristol-Myers Squibb Company, Bayer HealthCare Pharmaceuticals, Merck & Co., Inc., and Eli Lilly and Company.

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

Your personal information is being collected as part of this study. This information, or data, may be used by researchers at MD Anderson or shared with other researchers and/or institutions for use in future research.

Before being shared for future research, every effort will be made to remove your identifying information from any data. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

In some cases, all of your identifying information may not be removed before your data are used for future research. If this research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data.

Conflict of Interest

Consent Form Page 5 of 8

Dr. David Hong (Collaborator) has received compensation from Bayer Corporation as a Consultant. The financial interests are within the limits of the conflict of interest policy.

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson may be collecting and using your PHI. For legal, ethical, research, and safety-related reasons, the research team may share your PHI with:
   - The OHRP
   - The IRB and officials of MD Anderson
   - Bristol-Myers Squibb Company, Bayer HealthCare Pharmaceuticals, Merck & Co., Inc., and Eli Lilly and Company, who are sponsors or supporters of this study, and/or any future sponsors/supporters of the study
   - Individuals with appropriate access through the MD Anderson Translational Research Accelerator database
   - Study monitors and auditors who verify the accuracy of the information
   - Individuals who put all the study information together in report form

   Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it

B. Signing this consent and authorization form is optional but you cannot take part in this study if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible according to state and federal law. However, in some situations, health authorities could be required to reveal the names of participants.

   Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer of MD Anderson at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

E. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ Date/Time:
_____

STONE, COLTON

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ Date/Time:
_____

ASSENT OF MINOR

SIGNATURE OF MINOR

I have been told what I will be asked to do in this study.

I have been told that I do not have to be in this study. If I decide not to be in this study, no one will be mad at me. I may quit at any time, but if I do, I may need to take a different treatment.

I have had a chance to talk about the study and ask the study doctor questions. All of my questions have been answered. I agree to be in this study and do what I am asked to do so long as I want to stay in this study. I agree that the study doctor can put me on this study. By signing this paper, I am not giving up any of my legal rights. I have been given a copy of this document.

_____ Date/Time: _____

WITNESS TO THE ASSENT

I was present during the explanation of the research to be performed under this protocol. The child participant was also present. In my opinion, the child assented to participate in the research.

_____ Date/Time: _____

WITNESS TO CONSENT

Appendix C

Instruments used for Data Collection

Screening

Record ID

Screening Date:

MRN:

First name:

Last name:

Current status:
- ○ Pending
- ○ Active
- ○ Deceased
- ○ Lost (unable to reach)
- ○ Eligible-not approached
- ○ Ineligible
- ○ Dropped
- ○ Refused

Eligible-not approached
- ○ Maximum enrollment reached
- ○ Physician choice
- ○ Time constraint

Reason for Ineligibility
- ○ Disqualifying comorbidity
- ○ Incorrect age for study
- ○ Incorrect diagnosis for study
- ○ Incorrect treatment for study
- ○ Language barrier
- ○ Out of time frame
- ○ Active Psychiatric problem/psychosis
- ○ Cognitive impairment problem (dementia)

Dropped
- ○ Physician request
- ○ Participant request
- ○ Participant too ill

Refused
- ○ Not interested in research
- ○ Overwhelming condition
- ○ Time constraint
- ○ No particular reason

Notes:

This form was completed by:

(initials)

Patient Registration Information

Record ID _____

Registration Info

Registration Date: _____

MRN: _____

Registration First Name: _____

Registration Last Name: _____

CORe #: _____

Email Address: _____

Phone number: _____

Did the participant agree to a qualitative interview? ○ Yes ○ No ○ NA

Date Qualitative Interview Completed: _____

Original transcript:

Verified transcript:

Signature

This form was completed by: _____

Demographics Form

Please complete the survey below.

Thank you!

Demo Date Completed: _____

BASIC DEMOGRAPHIC INFORMATION

Date of Birth _____

Age _____

WARNING: Age is less than 18!
Please check Demo date and Birth date before continuing.

Gender ◯ Female ◯ Male

Marital Status

◯ Married
◯ Single
◯ Divorced
◯ Legally Separated
◯ Widowed
◯ Significant Other

Ethnicity

◯ Hispanic or Latino
◯ Not Hispanic or Latino
◯ Patient Refused
◯ Unknown

Race

◯ White or Caucasian
◯ Black or African American
◯ Asian
◯ Native Hawaiian or Other Pacific Islander
◯ American Indian or Alaskan Native
◯ Patient Refused
◯ Other
◯ Unknown

Race Other (Specify) _____

EDUCATION

Select only the highest grade completed:

- ○ 0
- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ 5
- ○ 6
- ○ 7
- ○ 8
- ○ 9
- ○ 10
- ○ 11
- ○ 12 (High School Diploma)
- ○ 13
- ○ 14
- ○ 15
- ○ 16 (College Graduate)
- ○ 17 (Graduate or Professional Training)

EMPLOYMENT STATUS

Select one that best describes your job status:

- ○ Employed outside the home, full-time
- ○ Employed outside the home, part-time
- ○ Homemaker
- ○ Retired
- ○ Medical leave of absence
- ○ Disabled due to illness
- ○ Unemployed
- ○ Refused
- ○ Unknown/Not Reported

Form Completion

This form was completed by:

_____

MDASI-Modified

Please complete the survey below.

Thank you!

MDASI Completion Date: _____

M. D. Anderson Symptom Inventory-Modified

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours.

Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your pain at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your fatigue (tiredness) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your nausea at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your disturbed sleep at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being distressed (upset) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your shortness of breath at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with remembering things at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with lack of appetite at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling drowsy (sleepy) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

10. Your having a dry mouth at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling sad at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your vomiting at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your numbness or tingling at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your dizziness at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your eye problems at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your fever or chills at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your headache at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your irritability at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your issues with balance at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your itching at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your joint stiffness/soreness at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your lack of energy at its WORST?	○	○	○	○	○	○	○	○	○	○	○
23. Your malaise/not feeling well at its WORST?	○	○	○	○	○	○	○	○	○	○	○
24. Your mouth/throat sores at its WORST?	○	○	○	○	○	○	○	○	○	○	○
25. Your muscle soreness/cramping at its WORST?	○	○	○	○	○	○	○	○	○	○	○
26. Your muscle weakness at its WORST?	○	○	○	○	○	○	○	○	○	○	○
27. Your pain in the abdomen at its WORST?	○	○	○	○	○	○	○	○	○	○	○
28. Your problem with teeth or gums at its WORST?	○	○	○	○	○	○	○	○	○	○	○
29. Your problems with concentrating at its WORST?	○	○	○	○	○	○	○	○	○	○	○
30. Your problems with feeling cold at its WORST?	○	○	○	○	○	○	○	○	○	○	○
31. Your problems with feeling hot at its WORST?	○	○	○	○	○	○	○	○	○	○	○
32. Your rash or skin changes at its WORST?	○	○	○	○	○	○	○	○	○	○	○

33. Your skin problems at its WORST?	○	○	○	○	○	○	○	○	○	○	○
34. Your weakness in arms or legs at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Did you intentionally leave any items blank? ○ Yes ○ No

If yes, please continue to the next page.

If no, please go back and finish the previous items.

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours?

Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
35. General activity?	○	○	○	○	○	○	○	○	○	○	◉
36. Mood?	○	○	○	○	○	○	○	○	○	○	○
37. Work (including work around the house)?	○	○	○	○	○	○	○	○	○	○	○
38. Relations with other people?	○	○	○	○	○	○	○	○	○	○	○
39. Walking?	○	○	○	○	○	○	○	○	○	○	○
40. Enjoyment of life?	○	○	○	○	○	○	○	○	○	○	○

Did you intentionally leave any items blank? ○ Yes ○ No

If yes, please continue to the next page.

If no, please go back and finish the previous items.

Form Completion

How was this form completed?

○ By the participant
○ By the study coordinator (over the phone or by interview)

Please draw signature with mouse or finger

FACT-M

Please complete the survey below.

Thank you!

FACT-M Completion Date: _____

Below is a list of statements that other people with your illness have said are important.

Please choose one number per line to indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

	0 - Not at all	1 - A little bit	2 - Somewhat	3 - Quite a bit	4 - Very much
I have a lack of energy	○	○	○	○	○
I have nausea	○	○	○	○	○
Because of my physical condition, I have troublemeeting the needs of my family	○	○	○	○	○
I have pain	○	○	○	○	○
I am bothered by side effects of treatment	○	○	○	○	○
I feel ill	○	○	○	○	○
I am forced to spend time in bed	○	○	○	○	○

SOCIAL/FAMILY WELL-BEING

	0 - Not at all	1 - A little bit	2 - Somewhat	3 - Quite a bit	4 - Very much
I feel close to my friends	○	○	○	○	○
I get emotional support from my family	○	○	○	○	○
I get support from my friends	○	○	○	○	○
My family has accepted my illness	○	○	○	○	○
I am satisfied with family communication about my illness	○	○	○	○	○
I feel close to my partner (or the person who is my main support)	○	○	○	○	○

Regardless of your current level of sexual activity, please answer the following question.If you prefer not to answer it, please mark this circle and go to the next section. ○ I prefer not to answer

0 - Not at all	1 - A little bit	2 - Somewhat	3 - Quite a bit	4 - Very much

I am satisfied with my sex life	○	○	○	○	○

EMOTIONAL WELL-BEING

	0 - Not at all	1 - A little bit	2 - Somewhat	3 - Quite a bit	4 - Very much
I feel sad	○	○	○	○	○
I am satisfied with how I am coping with my illness	○	○	○	○	○
I am losing hope in the fight against my illness	○	○	○	○	○
I feel nervous	○	○	○	○	○
I worry about dying	○	○	○	○	○
I worry that my condition will get worse	○	○	○	○	○

FUNCTIONAL WELL-BEING

	0 - Not at all	1 - A little bit	2 - Somewhat	3 - Quite a bit	4 - Very much
I am able to work (include work at home)	○	○	○	○	○
My work (include work at home) is fulfilling	○	○	○	○	○
I am able to enjoy life	○	○	○	○	○
I have accepted my illness	○	○	○	○	○
I am sleeping well	○	○	○	○	○
I am enjoying the things I usually do for fun	○	○	○	○	○
I am content with the quality of my life right now	○	○	○	○	○

ADDITIONAL CONCERNS

	0 - Not at all	1 - A little bit	2 - Somewhat	3 - Quite a bit	4 - Very much
I have pain at my melanoma site or surgical site	○	○	○	○	○
I have noticed new changes in my skin (lumps, bumps, color (colour))	○	○	○	○	○
I worry about the appearance of surgical scars	○	○	○	○	○
I have been short of breath	○	○	○	○	○
I have to limit my physical activity because of my condition	○	○	○	○	○
I get headaches	○	○	○	○	○
I have had fevers (episodes of high body temperature)	○	○	○	○	○

I have swelling or cramps in my stomach area	○	○	○	○	○
I have a good appetite	○	○	○	○	○
I have aches and pains in my bones	○	○	○	○	○
I have noticed blood in my stool	○	○	○	○	○
I have to limit my social activity because of my condition	○	○	○	○	○
I feel overwhelmed by my condition	○	○	○	○	○
I isolate myself from others because of my condition	○	○	○	○	○
I have difficulty thinking clearly (remembering, concentrating)	○	○	○	○	○
I feel fatigued	○	○	○	○	○

At the site of my melanoma surgery:

	0 - Not at all	1 - A little bit	2 - Somewhat	3 - Quite a bit	4 - Very much
I have swelling at my melanoma site	○	○	○	○	○
I have swelling as a result of surgery	○	○	○	○	○
I am bothered by the amount of swelling	○	○	○	○	○
Movement of my swollen area is painful	○	○	○	○	○
Swelling keeps me from doing the things I want to do	○	○	○	○	○
Swelling keeps me from wearing clothes or shoes I want to wear	○	○	○	○	○
I feel numbness at my surgical site	○	○	○	○	○
I have good range of movement in my arm or leg	○	○	○	○	○

Form Completion

How was this form completed?

○ By the participant
○ By the study coordinator (over the phone or by interview)

Please draw signature with mouse or finger

_____

Satisfaction

Please complete the survey below.

Thank you!

Completion date	_____
Do you feel the surveys you just completed adequately captured your treatment experience?	◯ Yes ◯ No
If No, please explain what is missing.	
Please draw signature with mouse or finger	_____

Charlson Comorbidity Index

Record ID _____

Date of CCI: _____

CHARLSON COMORBIDITY INDEX Instructions: Include conditions that occurred or were active during the last year unless otherwise indicated.

Concurrent Disease Status (Charlson)

- ☐ Myocardial Infarction (MI - one or more definite or probable MIs; must have been hospitalized and had enzyme changes)
- ☐ Congestive Heart Failure (CHF -must have had exertional or paroxysmal nocturnal dyspnea and responded to medication with symptomatic improvement)
- ☐ Peripheral Vascular Disease (PVD -intermittent claudication, untreated aortic aneurism,acute arterial insufficiency (AAI), gangrene, vascular bypass, repair, or prosthesis)
- ☐ Cerebrovascular Disease (history of stroke, other cerebrovascular accident, or transient ischemic attacks; does not include more than minor residual effects of stroke or cerebrovascular accident)
- ☐ Dementia (senile and pre-senile dementias)
- ☐ Chronic Pulmonary Disease (dyspnea with moderate activity despite treatment; dyspnea with slight or no activity regardless of treatment; requiring constant oxygen; CO2 retention; PO2 < 50%)
- ☐ Connective Tissue Disease (systemic lupus erythematous, mixed connective tissue disease, polymyositis, rheumatoid arthritis, polymyalgia rheumatica)
- ☐ Peptic Ulcer Disease (requiring treatment)
- ☐ Mild Liver Disease (chronic hepatitis; or cirrhosis without portal hypertension or bleeding)
- ☐ Moderate or severe liver disease (cirrhosis with a history of bleeding esophageal varices and portal hypertension)
- ☐ Diabetes (treated with insulin or oral antihyperglycemics and without end organ disease)
- ☐ Diabetes with end organ disease (retinopathy, nephropathy, neuropathy)
- ☐ Hemiplegia or paraplegia (including that caused by any cerebrovascular accident)
- ☐ Moderate or severe renal disease (requiring renal dialysis or transplant; uremia; serum creatinine > 3 mg%)
- ☐ Any non-metastatic malignant solid tumor (treated in the last 5 years- other than primary cancer)
- ☐ Leukemia (acute and chronic myelogenous leukemia, acute and chronic lymphocytic leukemia, polycytemia vera)
- ☐ Lymphoma (Hodgkin's disease, non-Hodgkin's lymphoma, lymphosarcoma, multiple myeloma, Waldenstrom's macroglobulinemia)
- ☐ Metastatic solid tumor (other than primary cancer)
- ☐ AIDS (definite or probable - includes AIDS-related complex)

Age group

- ○ < 50 (0)
- ○ 50-59 (+1)
- ○ 60-69 (+2)
- ○ 70-79 (+3)
- ○ 80-89 (+4)
- ○ 90-99 (+5)

Charlson Score: _____

Signature

This form was completed by: _____

Site of primary lesion:	◯ Scalp ◯ Extremity ◯ Trunk ◯ Unknown

Previous Treatment History

Did the participant receive previous treatment for melanoma? (other than current tx)	◯ Yes ◯ No
Did the participant receive surgery for melanoma?	◯ Yes ◯ No
Date of surgery:	_____
Type of surgery:	☐ Wide local excision (WLE) ☐ Sentinel node biopsy (SNB) ☐ Complete lymph node dissection (CLND) ☐ Resection
Any additional surgeries for melanoma?	◯ Yes ◯ No
Date of additional surgery:	_____
Type of additional surgery:	◯ Wide local excision (WLE) ◯ Sentinel node biopsy (SNB) ◯ Complete lymph node dissection (CLND) ◯ Resection
Did the participant previously receive immunotherapy?	◯ Yes ◯ No
Treatment regimen (check all that apply):	◯ Nivolumab ◯ Pembrolizumab ◯ Ipilimumab ◯ Ipilumab + Nivolumab ◯ Relatlimab + Nivolumab ◯ ICI Clinical Trial ◯ Other
If other, please specify:	_____
Date immunotherapy initiated:	_____
Date immunotherapy completed:	_____
Number of cycles completed:	_____
Did the participant previously receive radiation?	◯ Yes ◯ No

Date radiation initiated:	_____
Date radiation completed:	_____
Site of radiation:	◯ Primary ◯ Brain ◯ Lung ◯ Liver ◯ Adrenal ◯ Other
If other, please specify:	_____
Did the participant previously receive any other treatment (immunotherapy, interferon, etc.)?	◯ Yes ◯ No
Date other treatment initiated:	_____
Date other treatment completed:	_____

Current Treatment Information

What is the participants current immunotherapy? (check all that apply):	☐ Nivolumab ☐ Pembrolizumab ☐ Ipilimumab ☐ Ipilumab + Nivolumab ☐ Relatlimab + Nivolumab ☐ ICI Clinical Trial ☐ Other
If other, please specify:	_____
Date current immunotherapy initiated:	_____

Provider ROS

Provider ROS:	☐ Nurse ☐ APP ☐ MD
Nurse ROS:	
APP ROS:	

Final Status

Record ID	_____
Date of Final Study Status Form:	_____
Participant Initials:	_____
Is this patient evaluable for the study?	◯ Yes ◯ No (Baseline= Evaluable)
Date the patient went off:	_____
Reason patient went off:	◯ Patient's or clinician request ◯ Inability to contact the patient for 2 months ◯ Completion of the study ◯ Deceased ◯ Failure to complete baseline measure within 3 days of consent
Date the patient died:	_____
This form was completed by:	_____ (Initials)

MD ROS:

ECOG score

Evaluator:	◯ Assessed by Research Staff ◯ Assessed by Clinical Staff ◯ Not assessed
ECOG Performance Status now (Grade 0-5)	◯ Grade 0- Fully active, able to carry on all pre-disease performance without restriction ◯ Grade 1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work ◯ Grade 2- Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours ◯ Grade 3- Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours ◯ Grade 4-Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair ◯ Grade 5- Dead

Form Completion

This form was completed by:

_____

Disease and Treatment Information

Record ID

_____

DTI Completion Date:

_____

Disease History

Date of Diagnosis:

_____

TNM Stage at Diagnosis:

◯ Stage 0 ◯ Stage IA ◯ Stage IB ◯ Stage IIA ◯ Stage IIB ◯ Stage IIC ◯ Stage IIIA
◯ Stage IIIB ◯ Stage IIIC ◯ Stage IIID ◯ Stage IVA ◯ Stage IVB ◯ Stage IVC
◯ Stage IVD

Number of metastatic sites (check all that apply):

☐ Lymph node(s)
☐ Head
☐ Upper extremity
☐ Lower extremity
☐ Chest,
☐ Back
☐ Brain
☐ Lung
☐ Adrenal
☐ Bowel
☐ Other

If other, please specify:

_____

Current TNM Stage:

◯ Stage IIB ◯ Stage IIC ◯ Stage IIIA ◯ Stage IIIB ◯ Stage IIIC ◯ Stage IIID ◯ Stage IVA
◯ Stage IVB ◯ Stage IVC ◯ Stage IVD

Current number of metastatic sites (check all that apply):

☐ Lymph node(s)
☐ Head
☐ Upper extremity
☐ Lower extremity
☐ Chest,
☐ Back
☐ Brain
☐ Lung
☐ Adrenal
☐ Bowel
☐ Other

If other, please specify:

_____

Appendix D

Data (Excel spreadsheet)

Study #	Initials	ve intrevi	QI done	Stage	AGE	Gender	Race	ptoms on	therapy nam	ime on IC	adjuvant/metastatic
1	TB	N	N	IV M1d	49	M	White	yes	I + N	2.5 M	metastatic
2	MM	N	N	IV M1c	61	F	white	yes	I + N	1.5 M	metasatic
3	EM	Y	9/9/2022	IV M1c	82	M	white	yes	R + N	2 M	metastatic
4	MH	N	N	IV M1d	58	M	white	yes	Nivo*	10 M	metastatic
5	SK	Y	9/8/2022	IV M1b	66	F	white	yes	Nivo	3 M	metastatic
6	DP	Y	10/7/2022	IV M1c	74	F	white	no	R + N	5 M	metastatic
7	GR	N	N	IV M1b	73	M	white	yes	I + N (toci)	9M	metstatic
8	JR	N	N	II C	64	M	white	yes	pembro	6M	adjuvant
9	JM	N	N	IV M1b	80	M	white	yes	I + N	2 M	neo-adjuvant
10	SI	N	N	III C	32	M	white	yes	pembro	6 M	adjuvant
11	DW	Y	9/15/2022	IV M1a	48	F	white	yes	R + N	5 M	metastatic
12	JJ	Y	10/17/2022	IV M1b	66	M	white	yes	I + N	7m	metastatic
13	TS	N	NA	III B	57	M	white	yes	pembro	4 M	adjuvant
16	DD	Y	10/6/2022	IV M1c	55	F	white	no	R + N	5 M	metastatic
17	RK	Y	9/28/2022	IV M1c	71	F	white	yes	Nivo	9 M	metastatic
19	RP	N	N	IV M1c	65	M	white	no	I + N (toci)	4 M	metastatic
22	WJ	N	N	III B	61	M	white	yes	I + N	7 M	neoadjuvant/adjuvant
23	GK	N	N	IV M1c	76	F	white	no	Nivo	6 M	metastatic
24	RH	Y	10/11/2022	III D	59	M	white	yes	Nivo	8 M	adjuvant
25	IM	Y	10/23/2022	IV M1C	72	M	asian	no	Nivo*	10 M	metastatic
26	EC	Y	10/11/2022	III C	46	F	white	yes	I+N	1 M	neoadjuvant
27	JB	Y	10/24/2022	II B	55	F	white	yes	pembro	7M	adjuvant
28	JB	N	N	III A	46	M	white	yes	nivo	5 M	adjuvant
29	JF	N	N	III B	58	F	white	no	pembro	10 M	adjuvant
30	FY	Y	10/13/2022	IV M1b	74	M	Hispanic	yes	R + N	2 M	metastatic
31	MC	Y	11/11/2022	IV M1c	70	M	Black	no	I + N	3 M	metastatic
32	YA	N	N	IV M1c	52	F	Hispanic	no	R + N	4 M	metastatic
33	RG	N	N	III B	41	M	white	no	Nivo	10 M	adjuvant
34	YF	Y	10/24/2022	III B	51	F	Hispanic	yes	Nivo or R + N	6 M	adjuvant
35	LB	N	N	IV M1b	73	F	white	yes	Nivo	2 M	metastatic
36	KC	Y	10/24/2022	IV M1d	49	F	white	yes	Nivo*	10 M	metastatic
37	CT	N	N	IV M1 B	69	M	white	YES	pembro	9 M	metastatic
38	JR	N	N	III C	30	F	white	yes	Nivo	4 M	adjuvant
39	MD	N	N	III B	19	F	Asian	YES	Nivo	4 M	adjuvant
40	MP	N	N	IV M1C	60	F	white	yes	I + N	8 M	metastatic
41	MB	N	N	III C	75	M	white	NO	Nivo or R + N	2 M	adjuvant
42	LR	N	N	III B	63	F	white	NO	pembro	6 M	adjuvant
43	KC	N	N	III	36	F	White	NO	Nivo	5 M	adjuvant
44	MS	N	N	II B	76	F	white	yes	I + N	2 M	neoadjuvant
45	CW	N	N	III C	71	M	white	NO	Nivo	7 M	adjuvant
46	CH	N	N	IV M1a	74	F	white	yes	pembro	2 M	metastatic
47	WC	N	NA	II B	49	M	White	NO	pembro	5 M	adjuvant
48	SC	Y	2/2/2023	III B	34	F	White	yes	R + N	1 M	metastatic
49	CH	Y		IV M1C	78	M	white	NO	R + N	2 M	metastatic
50	RW	N	NA	IV M1b	61	F	white	yes	I + N	2 M	metastatic
51	RC	N	NA	IV M1C	52	M	white	Yes	Nivo	5 M	metastatic
52	WM	N	NA	IV M1D	47	M	white	NO	pembro	10 M	metastatic
53	KT	N	NA	IV M1c	64	M	white	yes	I + N	3M	metastatic
54	MT	N	NA	IV M1d	58	M	White	yes	I + N	3M	metastatic
55	JH	N	NA	IV M1b	59	F	White	yes	I + N	2 M	metastatic
56	DGC	Y		II B	65	F	white	yes	pembro	3 M	adjuvant
57	ST	Y	12/12/2022	IV M1D	38	F	white	yes	I + N	5 M	metastatic
58	LA	Y	12/6/2022	III B	67	M	white	yes	Nivo	9 M	adjuvant
59	DM	N	NA	IV M1B	71	M	white	yes	R + N	7 M	metastatic
60	LJ	N	NA	IV M1b	69	M	white	yes	R + N	1 M	metastatic
61	CB	Y		IV M1c	67	M	white	yes	I + N	1.5 M	metastatic
62	JP	N	NA	IIIA	70	M	white	yes	Nivo/ R + N	3 M	adjuvant
63	JK	N	NA	IV M1c	61	M	white	yes	Nivo	3 M	metastatic
64	AS	Y	12/12/2022	III b	42	M	white	no	Nivo	10 M	adjuvant
65	JW	N	NA	IV M1d	34	M	white	no	R + N	8 M	metastatic

Appendix E

Degree of Matching (Excel Spreadsheet)

Study #	Initials	ROS by c	on ROS by	on ROS	Symptoms on ROS	Symptoms in Chart by provide	art by provider (A	Symptom on MDASI	# sxs on MDASI	atch to MD	Symptoms on FACTM	of sx on FACT	h to FACT-M
1	TB	NA	5	NA	yes	etite, blurry vision, abdominal p	5	blems, fever, headache, i	28	5	lack of energy, nausea, fe	11	5
2	MM	NA	5	NA	yes	stipation, headache, and decre	5	uth, malaise, muscle we	14	5	lack of energy, nausea, pa	19	5
3	EM	2	7	NA	yes	hrlagias, neck pain, vomiting, c	7	ache, irritability, issues w	22	5	lack of energy, pain, feel i	15	5
4	MH	1	4	NA	yes	tivity, appetite change, fatigue,	4	es with balance, lack of e	7	4	lack of energy, disturbed :	4	1
5	SK	1	2	NA	yes	URI last week, diarrhea	2	ngling, eye problems, he	9	5	lack of energy, nausea, ne	8	5
6	DP	NA	0	NA	no	none	0	energy, mouth/throat so	9	5	lack of energy, skin chang	3	4
7	GR	2	NA	4	yes	rib pain from trauma, morning s	4	headache, irritability, issu	30	5	lack of energy, pain, feel r	9	5
8	JR	NA	1	NA	yes	rash	1	nce, joint stiffness/sore	8	5	pain at surgery site, aches	3	4
9	JM	NA	7	NA	yes	ck pain, mass growing, rash, w	7	ability, issues with balanc	31	5	lack of energy, pain, both	17	5
10	SI	ND	1	NA	yes	rash	1	ling upset, drowsy, sad, l	8	5	lack of energy, sad, nervo	6	5
11	DW	1	5	NA	yes	, constipation, lymphedema, ri	5	balance, itching, joint stif	29	5	lack of energy, nausea, pa	14	5
12	JJ	NA	3	NA	yes	cough, rash, itching	3	ching, joint stiffness, lac	20	5	lack of energy, pain, both	10	5
13	TS	NA	2	NA	yes	nosebleeds, insomnia	2	uth, dizziness, joint stiff	6	5	lack of energy, bothered b	7	5
16	DD	0	0	NA	no	none	0	s, dry mouth, itching, join	5	5	worry,	1	4
17	RK	0	2	NA	yes	gait problem, weakness	2	ues with balance, joint s	17	5	lack of energy, bothered b	8	5
19	RP	3	0	NA	yes	rash, arthritis	2	bility, joint stiffness/sore	10	5	worry, issues with sleep, f	3	4
22	WJ	2	NA	2	yes	nausea, SOB	2	mbness/tingling, irritabil	17	5	lack of energy, nausea, pa	10	5
23	GK	ND	2	NA	yes	cough, rash	2	y, issues with balance, it	31	5	lack of energy, nausea, pa	20	5
24	RH	NA	1	NA	yes	Slow urine stream post-op	1	sy, eye problems, lack o	7	5	lack of energy, issues sle	9	5
25	IM	1	1	NA	yes	vitiligo to the face	1	uth, eye problems, rash/s	4	4	skin changes, SOB,	2	4
26	EC	6	5	NA	yes	ue, rash, itching, dry eyes, dry s	5	s, fever/chills, headache	18	5	lack of energy, feel ill, sad	14	5
27	JB	NA	3	NA	yes	joint pain, back pain, diarrhea,	3	, itching, joint stiffness/s	23	5	lack of energy, bothered b	14	5
28	JB	NA	3	NA	yes	tigue, brain fog, memory chan	3	ith balance, lack of ener	33	5	lack of energy, pain, both	19	5
29	JF	NA	NA	0	no	none	0	none	0	1	sad, losing hope against i	8	5
30	FY	ND	4	NA	yes	vision, leg swelling, nausea, vo	4	ritability, issues with bala	8	5	lack of energy, nausea, pa	14	5
31	MC	1	5	NA	yes	tigue, decreased activity, fatig	5	lack of energy, malaise,	21	5	lack of energy, bothered b	10	5
32	YA	ND	1	NA	yes	nasal congestion	1	oint stiffness/soreness,	21	5	lack of energy, pain, both	15	5
33	RG	NA	0	NA	no	none	0	, irritability, lack of energ	28	5	lack of energy, nausea, pa	20	5
34	YF	3	2	NA	yes	cough, fatigue	2		0	2	lack of energy, nervous, v	6	5
35	LB	1	1	NA	yes	joint pain	1	wsy, dry mouth, sad, lack	11	5	lack of energy, forced to :	12	5
36	KC	5	8	NA	yes	tite, fever, UTI, HA, rash, dry lip	8	iritability, issues with bal	31	5	lack of energy, nausea, pa	20	5
37	CT	NA	3	NA	YES	nors, pain, nausea while in the	3	oness/tingling, joint stiff	8	5	pain, bothered by side effe	5	4
38	JR	0	1	NA	yes	fatigue	1	ep, drowsy, lack of energ	6	5	lack of energy, pain, sad,	7	5
39	MD	0	1	NA	YES	fatigue	1	bness/tingling, headach	11	5	lack of energy, pain, both	17	5
40	MP	1	0	NA	YES	none	0	ng, problems with feeling	2	4	bothered by side effects c	6	5
41	MB	0	0	NA	NO	none	0	nembering things, conce	2	4	skin changes, numbness	2	4
42	LR	NA	0	NA	NO	none	0	mouth, issues with bala	2	4	bothered by side effects c	3	4
43	KC	NA	0	NA	NO	none	0	nergy, irritability, concent	6	5	lack of energy, pain at sur	6	5
44	MS	ND	3	NA	yes	igue, left eye bulging, leg swelli	3	dry mouth, eye problems	2	2	lack of energy, bothered b	11	5
45	CW	1	0	NA	NO	none	0	, drowsy, lack of energy,	4	5	lack of energy, bothered b	9	5
46	CH	NA	0	NA	yes	none	0	aise, joint stiffness/sore	18	5	worry, limit physical activi	7	5
47	WC	0	1	NA	yes	rash	1	ergy, joint stiffness/sore	22	5	lack of energy, nausea, pa	15	5
48	SC	1	4	NA	yes	rash, fatigue, itching, hair loss	4	sad, irritability, lack of en	13	5	lack of energy, bothered b	14	5
49	CH	0	0	NA	NO	none	0	h remembering things, fe	2	4	aches in bones, concentr	2	4
50	RW	5	NA	3	YES	arrhea, stomach cramping, fev	3	oint stiffness/soreness,	14	5	lack of energy, nausea, pa	16	5
51	RC	2	4	NA	YES	rthralgias, weakness, sleep dis	4	oint stiffness/soreness,	24	5	lack of energy, nausea, pa	23	5
52	WM	NA	0	NA	NO	none	0	lems, headache, iritabilit	28	5	lack of energy, nausea, pa	18	5
53	KT	6	NA	7	YES	hea, abdominal pain, back pair	7	ance, lack of energy, ma	20	5	lack of energy, bothered b	15	5
54	MT	1	3	NA	yes	headache, fever, fatigue	3	ritability, lack of energy,	21	5	lack of energy, nausea, pa	24	5
55	JH	ND	2	NA	yes	rash, itching	2	tching, rash/skin change	4	4	bothered by side effects,	6	5
56	DGC	NA	4	NA	yes	adaches, neck pain, generalized	4	g things, fever, headach	10	5	lack of energy, nausea, pa	18	5
57	ST	2	3	NA	yes	flushing, diarrhea, vomiting	3	numbness/tingling, eye	16	5	lack of energy, nausea, bo	10	5
58	LA	2	2	NA	yes	chest congestion, rash	2	nergy, itching, rash/skin	3	4	worry	1	2
59	DM	0	2	NA	yes	skin changes, appetite change:	2	energy, malaise, joint st	23	5	lack of energy, pain, worry	12	5
60	LJ	2	2	NA	yes	brain fog, fatigue	2	, sad, headache, lack of	4	4	lack of energy, sad, nervo	7	5
61	CB	2	4	NA	yes	onstipation, headache, multiple	4	ffness/soreness, itching	11	5	lack of energy, pain, force	7	4
62	JP	6	NA	3	yes	diarrhea, rash, dry skin	3	owsy, lack of energy, ras	3	1	lack of energy, worry, imp	6	4
63	JK	2	2	NA	YES	cough, diarrhea	2	ility, lack of energy, mala	19	5	lack of energy, pain, both	11	5
64	AS	NA	0	NA	NO	none	0	drowsy, sad, headache, it	8	5	lack of energy, issues sle	9	5
65	JW	NA	NA	none	NO	none	0	none	0	1	worry, headaches,	2	4

Appendix F

Symptom and Interference organization

Symptom	Symptom	Symptom
Lost all the hair	Dry mouth	More emotional **Irritability**
Extra thirst	Dry skin (skin problems)	Couldn't get the IV-???
I have a lot of energy	Dry eye (**eye problems)**	Tough day-???
Couldn't move (lack of energy	Inside mouth peeling (**dry mouth)**	Tired (**lack of energy)**
Vitiligo	Life is pretty much the same (no interference)	Feel groggy **Malaise**
Nausea	Adrenal problem **(Endocrine dysfunction)**	Itching of the skin
Nausea and **vomiting**	Thyroid problem **(Endocrine dysfunction)**	Feel horrible (**Malaise)**
Financial impact-**(financial toxicity)**	Shortness of breath	Stabbing pains (**Pain)**
I feel great-shouldn't be in the category of sick people	Worry (**Anxiety)**	Joint pain (**Joint stiffness/ soreness)**
Cost of care as self pay **(financial toxicity)**	**Diarrhea**	Difficulty concentrating **(Brain fog)**
Parking costs **(financial toxicity)**	A little winded (**SOB)**	Feel a little but out of it **Brain fog**
Cost of frequent MD visits **(financial toxicity)**	Issues with prostate	Forget things a little easier-**remembering things**
	Sweating	No energy **(lack of energy)**
Financial impact-insurance doesn't cover 100% **(financial toxicity)**	I haven't' had any adverse reactions- **No symptoms**	Out of energy **lack of energy)**
		Chills
		fevers
Hot flashes (feeling hot)	No upset stomach- **No symptoms**	**Constipation**
Its hard to explain **(Nebulous feeling)**	No bowel issues- **No symptoms**	**Change in appearance**
Sensation of a "non-natural state" during infusion-like wow- **(Nebulous feeling)**	I haven't really felt any side effects- **No symptoms**	Emotional Rollercoaster- **Irritability**
	Feeling sad	Headache
Felt medicated- **(Nebulous feeling)**	Lack of symptoms- **No symptoms**	Moles- **Skin problems**
Feel foggy **(brain fog)**	Feeling drained (**lack of energy)**	Pain

Symptom	Symptom	Symptom
I had no energy (lack of energy)	No aches, pains, nothing- **No symptoms**	Feeling overwhelmed- (Distressed/upset)
itching	I feel normal- **No symptoms**	Uncertainty **(Fear of unknown)**
Numbness	No nausea **No symptoms**	Sleep problems- **disturbed sleep**
Numbness in the leg	No appetite loss- **No symptoms**	Couldn't breathe (SOB)
Swelling of leg due to tumor **(Swelling of extremity)**	No weight loss- **No symptoms**	Any time I get sick it ends up in my chest (pre-tx as well)
Muscle soreness	No weakness- **No symptoms**	**Cough**
Stiff neck	No diarrhea- **No symptoms**	Congestion in my lungs
dizziness	No fever- **No symptoms**	fatigue
New skin cancers from therapy (skin problems)	Still doing my social activities- **no interference**	Rash
		Neck pain (Pain)

Symptom Interference			
Couldn't take long trips due to diarrhea- Activity	Sx so bad I had to come to the hospital- Activity	Had to resolve current sx before starting new tx- **Inconvenient**	Able to exercise (activity)
Always sensitive to gluten but ICI made it made it worse- **Altered diet/food to eat**	Just takes more time= putting on lotion, eye drops, drink more water- **Inconvenient**	Not an annoyance, something that just happens every now and then- **Inconvenient**	Treatment and everything seem to be easy—**(lack of interference)**
Absolutely miserable- Enjoyment of life	Not worried about it, its not that bad	Hard to communicate due to dryness- Activity	Feels like one more thing I have to deal with- **Inconvenient**
Doesn't stop me from doing what I want to do/ I love the ability to be active- **(lack of interference**	Miss something at work (due to fogginess)- **Forget things at work/** Working	Skin changes, bothers me from due to vanity- **Personal/Vanity**	Schedule impacted, want to leave for work but diarrhea would hit- Activity
	Hasn't slowed me down any- **(lack of interference)**	Not interfering on my ability to get up and go to work- **(lack of interference**	No negative impact- **(lack of interference)**

Symptom Management			
Diet impacts my bowels-can control what I eat	Don't make plans that day except to rest/sleep		Inhaler
Biotine mouthwash	More sleep and less stress		Cholestyramine
Cough syrup	Cream stops the itch		Steroids
Eye drops			

Navigating Tx and healthcare system:		
ICI has shorter tx time	Do I know enough, am I asking the right questions	Just managing it all, figuring it all out
Organized appts all in 1 day	Stress of getting dx Stage IV then trying to get in to a doctor	Cost of treatment
Adjust schedule to miss less of kids stuff	Telehealth/use of regional centers is convenient	Appreciate the telehealth

PSYCHOLOGICAL SYMPTOMS

Symptom	Symptoms	Symptom
"nerves are up, don't know what's going on"- **Anxiety**	The mental part is aging me, not the treatment- **Anxiety**	I have to deal with it and I'm gonna deal with it- **Acceptance**
Glad [tx] is going well and my body hasn't "freaked out" again- **Positive thoughts on treatment**	More intimidating first diagnosed b/c I was young	Unknown response until scans are done- **Fear of unknown**
Willing to do anything to be here longer	I look at others and know I could have it so much worse- **Coping**	Have a little bit of powerlessness- **Lack of Control**
Disruptive to life	Cancer impacts not just me- Relations with other people	Lips sticking to teeth due to dryness- Activity
Angry	Self-conscious of symptoms- **Personal/Vanity**	Didn't want to be seen as different- **Personal/Vanity**
My **fear is dying** of this disease	Worry about cancer coming back **(anxiety)**	Nothing is guaranteed- **Acceptance of cancer**
Lack of control	Constantly worried **(anxiety)**	**Depression**
Can't process dying, suffering all of that- **Fear of suffering**	Just praying everything is going to be fine- **Faith**	I'm not comfortable with my situation- **Being distressed/ upset**
Anxiety	I get upset easily- **Irritability**	Feel aggressive- **Irritability**
Hope for the best- **Hopeful**	Have a good support system- Relations with other people	Coping by staying busy- **Coping**
Having some medical knowledge means I know too much - **Anxiety**	I'm pretty positive about it- **Hopeful**	I think treatment will shrink the tumor- **Positive thoughts on treatment**
	Optimistically naïve- **Hopeful**	
	Belief in God- **Faith**	
Hope they take control of [the cancer]- **Hopeful**	Just a lifelong thing I will have to deal with- **Acceptance**	Anxious about the future- **Anxiety**
		Prayer- **Faith**

Symptom	Symptoms	Symptom
Friends that give me encouragement- Relations with other people	Family that give me encouragement- Relations with other people	Would be nice to know where melanoma started
Petrified- **Scared**	Very good care	I'm kind of a scaredy-cat
Feel pretty fortunate	Attitude	Feel like I'm gonna beat this
Bizarre we don't know where it started	great determination to beat this	Scary not being on treatment*
I have no control and this is scary for me- **Lack of Control**	Willing to do anything to treat the cancer	**Not wanting to acknowledge cancer or give cancer power**
Relying on **faith**	"I'm a big Jesus believer"- **Faith**	Worry about family- **Anxiety**
Constantly thinking about cancer	Constant overwhelming **fear of death**	**Acceptance** of cancer
Worry about unknowns- **Fear of unknown**	Worry about death- **Anxiety**	Hope for the future- **Hopeful**
*= patient wasn't on therapy for a while in the past, is currently on ICI; Sx= symptoms; Tx= treatment		

Captured data

Get grief at work b/c people don't believe I have cancer	I go out of my way to look like I don't have cancer- **Personal/Vanity**	Concern if I don't have sx will it be too late and the cancer be "too much" to treat
Its been a lot easier than expected	Hope the tx works and gives me more years	How do you get rid of [melanoma] so you don't have to deal with it your whole life
I see so many people worse off than me	Appreciate the shorter treatment and less frequent visits	More conscious about sun protective behaviors-lotion, clothing, the time outside
I [patient] is not the only one impacted by cancer/tx- Relations with other people	I feel normal, except on paper I have cancer	Took understanding the risk of cancer coming back to pick to do adjuvant therapy
Sx haven't hurt but also haven't helped my QOL	Will do tx as long as sx don't make me a burden to others	As long I can move and not in excruciating pain, I'm ok with tx
My **fear is dying** of this disease	Chose ICI b/c I didn't want to have more surgery, friend told me to avoid at all costs	I cope with anxiety of cancer by submerging myself in work
Can handle the sx as long as I'm alive	Just tired of treatment, all the MD appts, lab draws- **Inconvenient**	I don't feel like I know what questions to ask
Overwhelmed about making the decision to do adjuvant tx	Feeling great, not bothered	Someone did research for me so I am happy to be able to do it for someone else
I believe research is very important	I believe I will see somewhat of a cure	I want to be cured
I feel I'm gonna be healed	Feel guilty for waiting so long to get it checked once I found out it was melanoma	More aware of moles and skin changes now that I've been diagnosed
Tough relying on MD as I'm used to relying on myself- **Lack of Control**	I just follow directions of my MD	

Initial Diagnosis:

- Bump on my head that wouldn't heal
- Only went to MD b/c my leg was swollen
- Was getting normal physical that included CT scan and they found it
- Getting regular eye exam and found it
- Family member said to go the bump checked out-didn't do it until they told me
- 1st provider at home actually missed the diagnosis
- Shocked by the diagnosis
    - Didn't look like any example of melanoma
    - "how is this even happening"
    - Disbelief of the diagnosis-not doubting just can't believe it
    - Devastated by the diagnosis

Things patients can control about sx

- Mind body connection
- Sun protection
- Physical activity
- nutrition

Reporting sx to provider

- I didn't b/c I assumed the sx were from sitting in a car too long (from normal stuff, not CA)
- Just stubbornness prevented me from calling
- I waited until I came to the provider b/c I knew I was coming
- Didn't call b/c I knew I was coming anyways to the MD
- If I say something [like pain] my family gets more excited than before ca dx
- **Not sure if sx are from tx, cancer or just normal life**
    - Stress may be causing it instead of tx
    - My husband was sick with the same sx so not sure that or tx
    - Not sure if last dose of ICI or swimming in chlorine that made it worse

Good thoughts on oncology care

- I’m a person, not a number
- Great communication about tx and plan of care
- If I stop therapy and eventually [cancer] comes back, I would come back to MDA
- Great doctor
- Gratitude for advances in tx options
- Couldn’t have more confidence than I do in my MDA docs
- Great staff and team
- “I call them my dream team”
- Wanted to get to MDA for treatment
- Team is always truthful and honest
- Nothing short of a miracle

Complaints on oncology care

- Doctors not asking about worries
- Only talk about the disease, not any other issues
- Thinks doctors could focus more holistically
- The food in the MDA cafeteria actually promotes cancer (sweets, fried food)
- Travel time to MDA
- Houston is scary and hard to navigate
- It just takes awhile to get a response from team
- Difficult to get a hold of team at MDA (phone)

Step 2. combined words

Physical symptoms

Pain	Fatigue	Nausea	disturbed sleep	Being distressed/ upset
SOB	remembering things	Lack of appetite	Drowsy	dry mouth
Sad/depression?	Vomiting	numbness/ tingling	Dizziness	eye problems
Fever	Headache	Irritability	Issues with balance	Itching
Joint stiffness/ soreness	lack of energy	Malaise	Mouth/throat sores	Muscle soreness/ cramping
Muscle weakness	Abdomen pain	Problem with teeth/ gums	Feeling cold	Feeling hot
Rash	Skin problems	weakness	Hair loss	Extra thirst
vitiligo	vomiting	Financial toxicity	Nebulous feeling	Brain fog
No symptoms	diarrhea	Swelling of extremity	Endocrine dysfunction	constipation
Change in physical appearance	Sweating	Cough	Lack of Control	Scared
Angry	Depression	Anxiety	Fear of unknown	Faith
Positive thoughts on treatment	Positive thoughts about provider	Negative thoughts about therapy	Negative thoughts about provider	Hopeful

Green is MDASI Core

Orange is MDASI Modified

Black is pulled from Cognitive interview only

Symptom interference

Walking	Activity	Working	Relations with other people	Enjoyment of life
mood	**Concentration**	**Forget things at work**	**Altered diet/food to eat**	**Inconvenient**
No interference	**Personal/Vanity**			

Coping

Hopeful

Fear of dying

Fear of suffering

Green is MDASI Core

Orange is MDASI Modified

Black is pulled from Cognitive interview only

CURRICULUM VITAE
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EDUCATION

University of Texas Houston, Texas	2023	PhD	Nursing
Texas Woman's University Houston, Texas	2011	MSN	Nursing
University of Texas Austin, Texas	2004	BSN	Nursing

PROFESSIONAL POSITIONS

The University of Texas MD Anderson Cancer Center
Melanoma Medical Oncology
Houston, TX
Family Nurse Practitioner 10/2011- present

St. Luke's Episcopal Hospital,
Cardiac Catheterization Lab
Houston, TX
Registered Nurse 03/2007- 10/2011

The University of Texas Medical Branch
Surgical/Overlfow Intensive Care Unit
Galveston, TX
Registered Nurse 02/2005-03/2007

Memorial Hermann Medical Center
Jones Medical Floor
Houston, TX
Registered Nurse 06/2004-02/2005

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LICENSURE AND CERTIFICATIONS

- Board Certified-National American Academy of Nurse Practitioners as a Family Nurse Practitioner 09/2011-current

- Registered Nurse, TX, 707117, 07/31/2016 07/2004-present

PROFESSIONAL MEMBERSHIPS

Southern Nursing Research Society 2019-present

American Academy Nurse Practitioners 2011-present

Oncology Nursing Society 2012-present

Houston Area Chapter 2019-present

Sigma Theta Tau International 2020-present

PUBLICATIONS

Contributing Author papers published as Natalie Jackson and my former name Natalie McQuail

Ahn, H., **Jackson, N.,** An, K., Filligim, R., Miao, H., Lee, M., Ko, J., Galle, K., & Lee, M., (2020, accepted). Relationship between acculturative stress and pain catastrophizing in Korean Americans. Journal of Immigrant and Minority Health. (Impact Factor = 1.8)

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Milbury, K., Whisenant, M., Weathers, S., Malliaha, S., Snyder, S., **Jackson, N**., Li, J., Li, Y., Silva, R.F., Shih T., & Cohen, L. (2022). Dyadic versus individual delivery of a yoga program for family caregivers of glioma patients undergoing radiotherapy: results of a 3-arm pilot, randomized controlled trial. *Cancer Medicine.* EPub ahead of print 5 December 2022.

Olsen, M., LeFebvre, K., Brassil. (2019) *Chemotherapy and Immunotherapy Guidelines and Recommendations for Practice* | ONS. https://www.ons.org/books/chemotherapy-and-immunotherapy-guidelines-and-recommendations-practice. Chapter 10 **(Jackson, N.)**

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Uemura, M., Fa'ak, F., Haymaker, C., **McQuail, N**., Sirmans, E., Hudgens, C. W., Barbara, L., Bernatchez, C., Curry, J. L., Hwu, P., Tetzlaff, M. T., & Diab, A. (2016). A case report of Grover's disease from immunotherapy-a skin toxicity induced by inhibition of CTLA-4 but not PD-1. *Journal for immunotherapy of cancer*, 4, 55. https://doi.org/10.1186/s40425-016-0157-6

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Grants

- Elizabeth W. Quinn Oncology, Research Grant Award, $1,000-Manuscript pending

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PRESENTATIONS

Oral Presentations

Jackson, N. (May 2017) Oncolytic viruses at Oncology Nursing Society 43rd Annual Congress. May 2017 in Denver, CO

Jackson, N. (November 2017) Presentation on Talimogene Laherparepvec (TVEC) at Global Academic Program

PRESENTATIONS (Cont'd)

Jackson, N. & Ngyuen, (November 2018) Presentation on *Disaster preparedness* at JADPRO Live in, Hollywood, FL

Jackson, N. (April 30, 2019) *Immunotherapy: an overview and update of current therapies. Cancer vaccines and oncolytic viruses* in Houston for the National GAP Conference

Jackson, N. (June, 2019) *Immunotherapy Webinar* for ONS aired August 2019.

Poster Presentations

Sberian, C., Abdel-Wahab, N., Fa'ak, F., Shoukier, M., Joseph, J., Safa, H., Jackson, N., James, M., Ludford, K., Suarez-Almazor, M., Al-Atrash, G., Abudayyeh, A., Diab, A. (2019, September) Use of Checkpoint Inhibitors (CPI) in Allogeneic Stem Cell Transplant Recipients: An Institutional Experience and A Systemic Review of the Literature. Poster presented at European Society of Medical Oncology meeting, Barcelona, Spain.

Jackson, N., Rodgers, T., John, I., Milton, D. R., Haydu, L.E., Amaria, R.N., Diab, A., McQuade, J. L., Patel, S. P., Tawbi, H., Wong, M.K.K., Davies, M.A., Glitza, I.C. (2021). Outcomes of BRAF mutant metastatic melanoma (MM) patients (pts) after cessation of targeted therapy (TT) with BRAF or BRAF/MEK inhibitor(i). Poster presented at American Society of Clinical Oncology meeting, Chicago, IL