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Persistent immune-related adverse events after cessation of checkpoint inhibitor therapy: Prevalence and impact on patients' health-related quality of life

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List of abbreviations

AI	non-ICI-induced autoimmune disease
APC	antigen-presenting cell
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen 4
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5D-5L
HRQoL	health-related quality of life
ICI	immune checkpoint inhibitor
IrAE	immune-related adverse event
LAG-3	lymphocyte-activation gene 3
MHC	major histocompatibility complex
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1

List of publications

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Schulz TU, Zierold S, Akcetin SL, Pesch G, French LE, Heinzerling L. Untersuchung zu Folgen der Autoimmunität im Hinblick auf Lebensqualität bei Patient*innen mit Checkpoint-Inhibitor-Therapie. 31. Deutscher Hautkrebskongress. 2021; Hamburg, Germany. (Poster presentation)

1 Introduction

1.1 Immune checkpoint inhibitors

After cardiovascular diseases, cancer is the second leading cause of death in the European Union. For people under 65, malignancies are even the most common cause of death (1). In 2020, about 4 million new cancer cases and 1.9 million cancer-related deaths were estimated to have occurred in Europe. The highest incidences included breast cancer, colorectal cancer, lung cancer, prostate cancer, bladder cancer, and melanoma (in descending order) (2). Due to the aging of the population and since cancer disproportionately affects elderly people, the incidence of cancer in European countries is expected to increase by 21% in 2040 compared to 2020 (3). Cancer results in a significant loss of years of life - with melanoma being one of the tumour entities with the highest average years of life lost per death (4).

For a long time, cancer therapies were limited to the therapeutic pillars of surgery, radiation therapy, and chemotherapy (5). Fortunately, modern medicine has made tremendous progress in combating oncological diseases in recent decades through the development of new drugs and innovative medical devices as well as the investigation of optimal therapeutic combinations (6). Among the most innovative anticancer drugs that have found entry into clinical use are targeted therapies and immunotherapies. While targeted therapies are directed against specific mutations and proteins of the tumour, which enable cancer cells to proliferate and spread (for example by modifications of the cell cycle or angiogenesis), immunotherapies use the body's own immune system's ability to fight the tumour cells (7).

Immunotherapies include various types of therapies that directly or indirectly stimulate, enhance, suppress, or desensitize components of the immune system which are relevant for the destruction of tumour cells. These therapies comprise immune system modulators, oncolytic viruses, cancer vaccines, T-cell transfer therapies, and immune checkpoint inhibitors (ICIs) (8). Particularly, ICIs have become an essential pillar of cancer therapy in the past years with a significant increase in clinical use for a wide variety of tumour entities (9).

1.1.1 Mechanisms of action

ICIs are monoclonal antibodies that block specific immune checkpoints and thereby induce anticancer immune responses. Physiologically, immune checkpoints control T cell activation through their ability to downregulate T cell responses. This system protects the body from overshooting and potentially damaging reactions, like autoimmune diseases. However, cancer cells can exploit this mechanism to their advantage by activating immune checkpoints and thereby inhibiting T cell responses, which leads to a compromised immune system with reduced anticancer defence. Hence, targeting and blocking specific immune checkpoint pathways can enhance anticancer immune responses and provide therapeutic benefits in cancer patients (10). ICIs currently approved by the European Medicines Agency (EMA) for the treatment of cancer comprise monoclonal antibodies that target the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), the programmed cell death protein 1 (PD-1), the programmed cell death ligand 1 (PD-L1), and the lymphocyte-activation gene 3 (LAG-3) (11). In 2018, the immunologists James P. Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine for their discovery of the immune checkpoints CTLA-4 and PD-1 as the basis for the development and use of ICIs (12).

CTLA-4 receptors are expressed on the surface of various types of T cells (T helper cells, cytotoxic T cells, and regulatory T cells). The activation of T cells occurs in interaction with antigen-presenting cells (APCs). Antigens are presented via the major histocompatibility complex (MHC) class II molecules of APCs and recognized by the T cell receptors. Simultaneously, the CD28 receptors of the T cells bind to the surface proteins CD80 or CD86 of the APCs, which has a signal modulating effect on T cell activation. The limitation of T cell activation is ensured by the CTLA-4 receptors of the T cells as they compete with the CD28 receptors for binding with the surface proteins CD80 and CD86. The administration of ICIs belonging to the monoclonal antibody class anti-CTLA-4 (such as ipilimumab and tremelimumab) blocks the CTLA-4 receptors and thus prevents the deactivation of the T cells (13).

PD-1 receptors are expressed by activated T cells, whereas their ligand PD-L1 is expressed on the surface of myeloid cells and cancer cells. The physiological role of the PD-1/PD-L1 pathway is to limit autoimmune responses by inducing apoptosis of antigen-specific T cells and diminishing apoptosis of regulatory T cells (14). Cancer cells exploit the immune checkpoint by upregulating PD-L1 to evade the immune system. Anti-PD-1 antibodies (such as nivolumab and pembrolizumab) and anti-PD-L1 antibodies (such as

atezolizumab and durvalumab) inhibit the pathway and thus facilitate the activation and survival of T cells for anticancer reactions (15, 16).

LAG-3 receptors are also expressed on the surface of activated T cells. The LAG-3 pathway limits T cell proliferation and negatively regulates the function of T helper cells. Ligands of LAG-3 (like MHC class II molecules or fibrinogen-like protein 1) are - similarly to PD-L1 - overexpressed in a wide variety of cancer cells, which enhances tumour-mediated T cell exhaustion. The monoclonal antibody relatlimab is used to block LAG-3 receptors (17, 18).

1.1.2 Use in melanoma therapy

Melanoma results from genetic mutations in melanocytes, which are the pigment-producing cells in the body. As melanocytes are of neuroectodermal origin, the cells are mainly located in the skin but also in the iris, the mesencephalon, or the mucosa. The major risk factors of melanoma are exposure to UV-radiation and sunburns, especially in childhood. Further risk factors include fair skin type, positive family history, previous melanomas, and the number and size of existing nevi (19, 20).

In early stages, melanoma is treated and often cured by surgery with adequate safety margins. Melanomas that are locally advanced or metastatic disease are associated with high mortality and require systemic therapies (21). For a long time, the chemotherapeutic agent dacarbazine was the standard of therapy in stage IV disease with less than 5% complete responses and a poor 5-year survival in 2% to 6% of patients (22). In the 1990s, immune system modulators such as peg-/interferon α-2b and interleukin-2 found their way into clinical use but were also limited in terms of overall survival (OS) (except for intralesional interleukin-2 with considerable benefits in a subgroup of patients) alongside notable side effect profiles (23, 24).

Since the early 2010s, melanoma therapy had been revolutionized by the introduction of the first targeted therapeutics, the BRAF and MEK inhibitors, and by the approval of the first ICI, ipilimumab (anti-CTLA-4 antibody) (23): in a phase 3 trial published in 2010, pre-treated patients with progressive unresectable stage III or IV melanoma were randomized to receive either ipilimumab as monotherapy, ipilimumab in combination with a gp100 peptide vaccine, or the vaccine as monotherapy. Ipilimumab monotherapy demonstrated the highest response rate with a median OS of 10.1 months, followed by ipilimumab plus gp100 peptide vaccine with a median OS of 10.0 months, and the vaccine monotherapy with a median OS of 6.4 months (25, 26). Melanoma was the first disease where ICI efficacy had been impressively demonstrated.

In the years that followed, numerous trials had been conducted and further ICIs were approved, with significantly improved outcomes compared to pre-ICI therapies: The anti-PD-1 antibody nivolumab was approved as monotherapy or in combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma and as adjuvant monotherapy for the treatment of melanoma with lymph node involvement or metastatic disease after complete resection. Notably, the OS at 5 years for patients treated with nivolumab plus ipilimumab was 52% (27-29). Additionally, pembrolizumab (anti-PD-1 antibody) was approved for the treatment of advanced (unresectable or metastatic) melanoma, interestingly also as adjuvant therapy in the earlier stages IIB, IIC, and stage III melanoma with lymph node involvement after complete resection (30-33). In 2022, the first LAG-3 inhibitor, relatlimab, was approved in combination with nivolumab as a first-line treatment for advanced (unresectable or metastatic) melanoma with tumour cell PD-L1 expression < 1% (17).

Further development and testing of ICIs for use in melanoma continues to be very dynamic. A growing number of studies is offering ICI therapies to patients with early-stage tumours. An example is the NivoMela study, which provides adjuvant treatment with nivolumab for melanoma patients in stages IIA to IIC (34).

1.1.3 Approved substances and indications

With ipilimumab as the first EMA-approved ICI for advanced melanoma in the year 2011, the way was paved for further approvals of numerous substances and various cancer types (see table 1) (11). Throughout the years, clinical use of anti-PD-1/PD-L1 antibodies has far surpassed that of anti-CTLA-4, due to higher clinical efficacy and better tolerability (35). ICIs are mainly indicated for solid tumours but are also permitted for liquid tumours such as nivolumab or pembrolizumab for classical Hodgkin lymphoma. Within the United States, the estimated proportion of cancer patients eligible for ICI therapies increased from 1.5% in 2011 to remarkable 43.6% in 2018 (9).

Considering the development of the number of ongoing clinical trials with ICIs, it becomes apparent that the approval and indication of ICIs in cancer therapy will continue to increase in the next years. Clinical trials investigating PD-1/PD-L1 inhibitors as monotherapy or in combination with other therapies grew by 278% over the past 5 years to a current total of 5,683 clinical trials in 2022 (36). In addition, there are several immune checkpoints that are being further explored and may lead to new ICIs. These include TIGIT, TIM3, B7H3, CD39, and CD73 (35). The conduct of numerous registration trials is encouraged by the high financial attractiveness of ICIs for the pharmaceutical industry.

In 2021, pembrolizumab and nivolumab ranked among the global top 10 best-selling drugs with US$17.2 billion and US$7.6 billion, respectively (37).

Table 1
ICIs: EMA-approved substances and indications (12/2022).

Monoclonal antibody	Substance	Date of initial approval	Indication
Anti-CTLA-4	Ipilimumab	07/2011	MEL
Anti-PD-1	Nivolumab	06/2015	MEL, NSCLC, RCC, cHL, HNSCC, UC, OSCC, OC, GEJC, GC
	Pembrolizumab	07/2015	MEL, NSCLC, cHL, UC, HNSCC, RCC, CRC, OC, GEJC, GC, BC, TNBC, EC, CC
	Cemiplimab	05/2019	CSCC, BCC, NSCLC
	Dostarlimab	04/2021	EC
Anti-PD-L1	Atezolizumab	09/2017	UC, NSCLC, SCLC, HCC, TNBC
	Avelumab	09/2017	MCC, RCC, UC
	Durvalumab	09/2018	NSCLC
Anti-CTLA-4 plus anti-PD-1	Ipilimumab plus nivolumab	05/2016	MEL, RCC, NSCLC, MPM, CRC, OSCC
Anti-PD-1 plus anti-LAG-3	Nivolumab plus relatlimab	09/2022	MEL

Anti-CTLA-4, anti-cytotoxic T lymphocyte-associated antigen 4; anti-LAG-3, anti-lymphocyte-activation gene 3, anti-PD-1, anti-programmed cell death protein 1; anti-PD-L1, anti-programmed cell death ligand 1; BC, biliary cancer; BCC, basal cell carcinoma; CC, cervical carcinoma; cHL, classical Hodgkin lymphoma; CRC, colorectal cancer (mismatch repair deficient or microsatellite instability-high); CSCC, cutaneous squamous cell carcinoma; EC, endometrial carcinoma; GC, gastric cancer; GEJC, gastroesophageal junction cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; MCC, Merkel cell carcinoma; MEL, melanoma; MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer; OC, oesophageal cancer; OSCC, oesophageal squamous cell carcinoma; RCC, renal cell carcinoma; SCLC, small cell lung cancer; TNBC, triple negative breast cancer; UC, urothelial carcinoma. Based on (11).

Previous studies have shown that CTLA-4 inhibition has a response rate of up to 20% in metastatic melanoma. However, outside of melanoma, anti-CTLA-4 monotherapy seems to have very limited activity (25, 38). In contrast, anti-PD-1/PD-L1 antibodies revealed clinical activity in different cancer types. Response rates range from 10-30% mainly in carcinogenic tumours (such as liver, bladder, and kidney cancer) to 40-50% in melanoma, highly PD-L1-positive non-small cell lung cancer, and cancers with high microsatellite instability or deficient mismatch repair. In classical Hodgkin's lymphoma, response rates of up to 75% are possible (39, 40). Besides, the combination of anti-CTLA-4 antibodies and anti-PD-1 antibodies can be very effective, with response rates of about 40% in renal cell carcinoma and up to 59% in metastatic melanoma (41-43).

Fortunately, the increasing number of approvals of ICIs and the high efficacy of ICIs - even with durable responses in metastatic diseases (44) - lead to a growing group of cancer survivors, who had been treated with ICIs.

1.2 Immune-related adverse events

As the administration of ICIs interferes with the physiological role of immune checkpoints, which is to prevent overactive immune reactivity, the downside of ICI therapies are the associated side effects induced by excessive immune responses, known as immune-related adverse events (irAEs) (35).

IrAEs can potentially affect any organ in the body, ranging from a mild skin rash to a life-threatening myocarditis with high fatality rates (45). Depending on their severity, irAEs are classified according to the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE categorizes adverse events from grade 1 to grade 5, which refers to mild, moderate, severe, life-threatening, or fatal irAEs (46). A meta-analysis of 36 phase II and III randomized controlled trials estimated a pooled incidence of irAEs at all severity grades ranging from 54% to 76% (47). IrAEs vary in frequency and severity depending on the type of ICI used, with anti-PD-1/PD-L1 antibodies generally having a more favourable safety profile than anti-CTLA-4 antibodies. In a randomized double-blind phase III study among patients with unresectable stage III or IV melanoma, treatment with ipilimumab caused severe irAEs (grade 3 or 4) in 27.3% of patients whereas treatment with nivolumab caused severe irAEs in only 16.3% of patients. Patients who were treated with ipilimumab plus nivolumab combination therapy experienced a notably higher incidence of severe irAEs with 55.0% of patients (48). Furthermore, depending on the type of ICI, some organs are more likely to be affected by side effects. While CTLA-4 inhibition typically induces more often hypophysitis or severe colitis, PD-1/PD-L1 inhibition more frequently causes thyroiditis, pneumonitis, or nephritis (45, 49).

As CTLA-4 and PD-1/PD-L1 pathways are also involved in the pathogenesis of non-ICI-induced autoimmune diseases (AIs), irAEs commonly mimic AIs such as autoimmune hypothyroidism, polymyalgia rheumatica, or rheumatoid arthritis (38, 50).

1.2.1 Onset and types

Depending on the organ system affected, irAEs typically occur within 2 to 16 weeks after initiation of ICI therapy. Nevertheless, irAEs may also appear within a few days after therapy start or develop even more than 1 year after therapy cessation. In the first four

weeks after the initiation of therapy, the probability of a first-time onset of irAEs is three times higher than after the first four weeks until the end of therapy. For both CTLA-4 inhibitors and PD-1 inhibitors, dermatological side effects are the most common irAEs within the first 12 weeks after initiation of therapy (10).

Organ systems frequently affected by side effects of ICI therapy include the skin, the gastrointestinal system, the endocrine organs, the lungs, and the musculoskeletal system (51). Cutaneous irAEs include a wide variety of manifestations with maculopapular rash, pruritus, psoriasiform rash, eczema, and lichenoid eruptions most common. Less frequent cutaneous irAEs are bullous pemphigoid, vitiligo-like skin hypopigmentation/depigmentation (which is associated with a better outcome for patients with advanced melanoma), alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms. Cutaneous irAEs affect between one third and more than half of all patients receiving ICIs. About 2% to 10% of all treated patients experience severe cutaneous irAEs (grade ≥3) (52, 53). Besides, irAEs of the gastrointestinal system are frequently reported. Diarrhoea is a very common symptom, occurring most commonly when ipilimumab is used as monotherapy (about 35% of patients) or in combination with nivolumab (about 45% of patients). Colitis is diagnosed less frequently (up to 14% of patients receiving combination therapy), partly because colonoscopy is not performed as a standard diagnostic procedure for ICI-induced diarrhoea (54, 55). Since the entire gastrointestinal tract may be affected, a gastritis or enteritis may also occur. Furthermore, the liver may show a (commonly asymptomatic) elevation of transaminases, indicating a (beginning) hepatitis (45). The exocrine pancreas can also be affected, usually with elevated lipase levels. However, in about 70% of cases with increased lipase levels, a pancreatitis is not evident (56). Moreover, the salivary glands can be inflamed, resulting in an underproduction of saliva with associated xerostomia (57). Endocrine irAEs comprise thyroiditis (which typically leads to hypothyroidism), hypophysitis (which mainly results in insufficiency of the corticotropic and/or thyrotropic axis), adrenalitis (which commonly leads to adrenocortical insufficiency), and type 1 diabetes mellitus. Endocrinopathies are reported in 4% to 14% of patients treated with PD-1 inhibitors and in up to 10% of patients receiving CTLA-4 inhibitors (10). Besides pneumonitis as the most common pulmonary irAE, patients may be affected by sarcoid-like granulomatosis or pleuritis. Whereas pneumonitis is rarely induced by CTLA-4 inhibitors, it is more frequently observed when PD-1 inhibitors are used (1% to 5% of treated patients). Pneumonitis can be a life-threatening complication, especially for patients with pre-existing pulmonary diseases (45). Furthermore, ICIs can induce irAEs in the musculoskeletal system in the sense of rheumatological irAEs. Common manifestations are arthritis, arthralgia, myositis,

myalgia, enthesitis, and polymyalgia rheumatica-like syndromes. Articular irAEs usually occur late, at a median of 70 days after onset of ICI (10).

Less commonly reported irAEs comprise neurological irAEs (such as encephalitis, aseptic meningitis, myasthenia gravis, and polyneuropathy), cardiac irAEs (such as myocarditis and pericarditis), renal irAEs (such as tubulointerstitial nephritis and glomerulonephritis), ocular irAEs (such as conjunctivitis, scleritis, uveitis, and xerophthalmia), and haematological irAEs (such as anaemia and neutropenia), among others (58-60).

1.2.2 Clinical management and resolution

Depending on the type of irAE and the grade of severity according to the CTCAE, ICI therapy may be interrupted or terminated, and immunosuppressive drugs may be administered. Various organizations have developed treatment guidelines to ensure efficient diagnosis and treatment of irAEs. First-line immunosuppressive agents are typically corticosteroids. As second-line therapy, other immunosuppressive agents are usually used, mainly belonging to the group of disease-modifying anti-rheumatic drugs (61-63).

In most cases, irAEs resolve with prompt and guideline-based therapy. For instance, irAEs of the gastrointestinal system or pulmonary irAEs are usually clinically manageable and reversible. However, depending on the organ system affected, irAEs may remain and develop a persistent condition. Endocrine irAEs are usually persistent and require lifelong hormone replacement. Among dermatologic side effects, the vitiligo-like skin hypopigmentation/depigmentation is typically irreversible and becomes a lifelong condition. Moreover, some musculoskeletal or rheumatological irAEs also tend to turn into a chronic condition. The same applies to neurological irAEs, with peripheral neuropathy most likely to leave residual effects (38, 64).

Since most ICI clinical trials stop recording adverse events a few months after ICI cessation, patients with ongoing toxicities and potential persistent irAEs are usually underreported and not specified (65). In the literature, there is only a very limited selection of studies on the prevalence or incidence of persistent irAEs. In a study of 217 cancer patients after anti-PD-1/PD-L1 therapy cessation, most commonly persistent irAEs observed were hypothyroidism (10.6% of patients), arthritis (3.2% of patients), adrenal insufficiency (3.2% of patients), and neuropathy (2.8% of patients) (66). Another study of 387 melanoma patients treated with adjuvant anti-PD-1 therapy revealed that, twelve weeks after therapy discontinuation, 43.2% of all patients still had at least one persistent irAE. The most common persistent irAEs reported were hypothyroidism

(14.0% of patients), arthralgias (5.7% of patients), dermatitis/pruritus (6.6% of patients), and adrenal insufficiency (3.1% of patients) (67).

1.3 Health-related quality of life in cancer patients treated with immune checkpoint inhibitors

Due to the increasing number of cancer patients, approved ICIs, and tumour entities eligible for ICIs, the group of cancer patients treated with ICIs is steadily increasing. Fortunately, the group of cancer survivors is also growing thanks to the high efficacy of ICI therapies, in some cases with enduring remissions. Besides the efficacy of ICI therapies, the patients' health-related quality of life (HRQoL) during and after treatment is a crucial parameter for a comprehensive evaluation of this innovative therapy.

Data on the HRQoL in patients treated with ICIs are obtained and evaluated regularly as part of the clinical trials. A meta-analysis comprising HRQoL assessments from 26 clinical trials demonstrated that ICI-treated patients had higher HRQoL than patients treated with other anticancer drugs. Moreover, no significant decrease in global HRQoL was observed during treatment (68). In contrast, other studies reported significantly reduced HRQoL in patients treated with ICIs compared to the general population (69, 70), as well as increased psychological morbidity and possible effects on cognitive functions (71, 72).

Studies examining HRQoL in patients exclusively after completion of ICI therapy are rare. A cross-sectional study with chart review of 90 long-term survivors of advanced melanoma after completion of ICI therapy (with a median of 28 months after ICI discontinuation) concluded that HRQoL was excellent despite problems with anxiety/depression in 40% of patients and pain/discomfort in 31% of patients. Furthermore, 17% of the patients stated that they still suffered from arthralgias and 12% of patients reported myalgias (73). Another study examined the impact of persistent irAEs on the HRQoL in 217 cancer patients (with melanoma, renal cell carcinoma, or non-small cell lung cancer) after discontinuation of anti-PD-1/PD-L1 therapy. No significant differences were found using two cancer-specific instruments (National Comprehensive Cancer Network Distress Thermometer; Functional Assessment of Cancer Therapy - General) and a posttraumatic instrument (Impact of Event Scale - Revised) (67).

1.4 Research questions of the publication

Since the number of cancer patients treated with ICIs is considerably increasing and, fortunately, the number of ICI-treated cancer survivors is also constantly growing, it is necessary to comprehensively investigate the situation of this group after therapy cessation regarding potential persistent side effects and their impact on the HRQoL.

Therefore, the publication on which this dissertation is based examined the following main research questions (74):

(1) What is the proportion of cancer patients affected by persistent irAEs after ICI discontinuation and which types of irAEs are present?

(2) What impact does the presence of persistent irAEs have on cancer patients' HRQoL?

(3) To what extent does the impact of persistent irAEs on cancer patients' HRQoL differ from the impact of comparable spontaneous AIs?

(4) Are there differences in the therapy of persistent irAEs compared to the therapy of spontaneous AIs?

(5) How do cancer patients evaluate ICI patient education in retrospect, depending on the presence of persistent irAEs?

1.5 Results of the publication

To investigate the research questions, a multicentre questionnaire-based cross-sectional study was conducted from April to October 2021 (74). Cancer patients with ICI discontinuation ≥12 weeks ago (ICI-patients) and patients with various spontaneous AIs (AI-patients) were recruited in German outpatient clinics and support groups. A total of 200 ICI-patients and 2705 AI-patients met inclusion criteria and submitted complete questionnaires.

Within the group of ICI-patients from outpatient clinics, which was an approximately representative group for German skin cancer centres' ICI-patients, 41.5% of patients reported at least one persistent irAE at the time of survey completion. Broken down by time since ICI discontinuation, persistent irAEs affected 51.9%/35.5% of patients <12/≥12 months since therapy cessation. The following prevalences of persistent irAEs were observed among all outpatient ICI-patients: arthralgia (16.3%), myalgia (13.6%), hypothyroidism (10.9%), vitiligo (9.5%), hypophysitis (8.2%), xerostomia (8.2%), pneumonitis/respiratory distress (4.8%), colitis (3.4%), dermatitis/pruritus (2.7%),

leukotrichia (2.7%), lichen ruber (2.7%), polyneuropathy (2.0%), diabetes mellitus (1.4%), adrenal insufficiency (1.4%), neuropathy of the cranial nerve VIII (0.7%), pancreatitis (0.7%), and hepatitis (0.7%). HRQoL was evaluated with the standardised patient-reported outcome measure EuroQol 5D-5L (EQ-5D-5L) comprising the EQ-Index score and the EQ-VAS score. ICI-patients with persistent irAEs reported significantly lower HRQoL than ICI-patients without persistent irAEs (subdivided by <12/≥12 months since ICI cessation: EQ-Index score: 0.767/0.752 versus 0.920/0.923, $p < 0.001/0.001$; EQ-VAS score: 52.2/52.0 versus 63.6/74.7, $p =/< 0.040/0.001$). Differences in EQ-5D-5L scores exceeded minimally important differences and indicated clinically meaningful changes. Moreover, multiple linear regression analyses also showed clinically significant reductions in HRQoL scores due to persistent irAEs in the group of ICI-patients ≥12 months since ICI cessation (EQ-Index/VAS score: -0.163/-23.4, $p < 0.001/0.001$). Furthermore, HRQoL in ICI-patients with persistent irAEs ≥12 months since ICI cessation was compared to HRQoL in AI-patients. It was showed that the impact of persistent irAEs on HRQoL scores was comparable to the impact of (resembling) non-exacerbated AIs. In addition, analysis of autoimmunity therapy showed a deficiency in the treatment of persistent irAEs for ICI-patients ≥12 months since ICI cessation: whereas ICI-patients received a mean of 0.61 medications per autoimmune symptom, the mean for AI-patients was with 1.07 significantly higher ($p < 0.001$). Among ICI-patients ≥12 months since ICI discontinuation, patients with persistent irAEs felt less well informed about side effects by patient education than patients without persistent irAEs (difference in agreements: -15.4%, $p < 0.001$).

In summary, it was revealed that after the end of ICI therapy a substantial proportion of patients is still affected by persistent irAEs and that persistent irAEs lead to a significant reduction in HRQoL.

1.6 Contribution to the publication

In the following I describe my contribution to the publication (74) on which this dissertation is based.

Initially, I conducted an extensive literature research regarding ICI therapy, irAEs, and HRQoL (in cancer patients). Based on the research questions, I conceptualized the questionnaires (one questionnaire for ICI patients and one questionnaire for AI patients) with assistance. The questionnaires were pretested by me on a selected group of persons to detect possible incomprehensibilities and to ensure the accuracy of questions. Subsequently, I incorporated the results of the pre-test into the questionnaires and finalized them. I then assisted in the application process for approval by the Ethics

Committee at the Medical Faculty of LMU Munich. From April to October 2021, I identified eligible ICI-patients at the Department of Dermatology and Allergy of the LMU Hospital in Munich by daily review of the outpatient list. The identified patients were usually contacted by me and invited to participate in the study. Furthermore, I was contact person for the participating outpatient clinics (Department of Dermatology, University Hospital Schleswig-Holstein, Kiel; Department of Dermatology, Allergology and Phlebology, Hospital Bremerhaven Reinkenheide, Bremerhaven; Department of Medicine IV, LMU Hospital, Munich). In addition, I designed the questionnaires as online questionnaires and contacted numerous support groups for ICI-patients as well as for AI-patients and invited them to participate in our study. I reviewed the collected questionnaires for compliance with the inclusion criteria and for completeness. Appropriate paper-based questionnaires were entered by me into a database. I also added the collected data from the online questionnaires to this database. After completing the survey, I performed the statistical analyses using the program SPSS Statistics (IBM®, version 28.0). I applied various methods of descriptive and mathematical statistics (among others Chi-square tests, Fisher's exact tests, Mann-Whitney tests, unpaired t-tests, binomial logistic regression analysis, multiple linear regression analyses). After that I created the tables as well as the figures. In parallel, I wrote the first draft of the manuscript. I adapted the first draft to the requirements of the journal and created a graphical abstract. Before submission, I incorporated the co-authors' corrections and changes. After the review, I implemented - with assistance - the requests of the reviewers. For this purpose, I carried out extensive statistical analyses again.

2 Summary

2.1 Summary in English

The introduction of ICIs for the treatment of malignancies has revolutionized oncology. ICIs block specific immune checkpoints and enhance the body's immune system, enabling it to better fight tumour cells, partly with durable remissions. Initially used in the treatment of melanoma, ICIs are today used in an increasing number of tumour entities – and the trend is rising. Encouragingly, a growing group of cancer survivors treated with ICIs is emerging. ICIs' mechanisms of action allow unprecedented responses for certain tumour entities, but also cause side effects triggered by the overactivated immune system, known as irAEs which commonly mimic AIs. Although most irAEs are reversible by pausing or discontinuing ICIs and/or administering immunosuppressants, several irAEs will persist. Typically, these are endocrinological irAEs, as well as some cutaneous, rheumatological, or neurological irAEs. Only very few studies had been conducted on persistent irAEs after discontinuation of ICI therapy and their impact on cancer survivors' lives.

The publication on which this dissertation is based examined the situation of ICI-treated cancer survivors regarding the prevalence of persistent irAEs and their impact on patients' HRQoL as well as the burden of autoimmunity due to symptoms and related therapies compared to (corresponding) AIs. From April to October 2021, a multicentre cross-sectional survey study was carried out at outpatient clinics (at the skin cancer centres of the LMU Hospital in Munich, the University Hospital Schleswig-Holstein in Kiel, and the Hospital Bremerhaven Reinkenheide in Bremerhaven, as well as at a department of internal medicine of the LMU Hospital in Munich) and via support groups (for cancer patients and patients with AIs). ICI-patients (≥12 weeks since ICI discontinuation) and AI-patients were surveyed with specific ICI-/AI-questionnaires including overlapping questions on patient demographics, HRQoL (EQ-Index/VAS scores), persistent symptoms of (ICI-induced/non-ICI-induced) autoimmunity and their burden, as well as related therapies and their burden. Out of all submitted questionnaires (paper-based or online), a total of 200 ICI-questionnaires and 2705 AI-questionnaires were evaluable and included in the statistical analyses (comprising descriptive- and mathematical-statistical methods) conducted with the program SPSS Statistics (IBM®, version 28.0).

Most ICI-patients were diagnosed with melanoma (96.5%), reported advanced disease (98.0%), and had a complete response (67.5%) due to anticancer therapies. Pembrolizumab (41.0%), nivolumab (39.5%), and ipilimumab plus nivolumab (29.5%)

were most frequently reported therapy regimens, with a median time since ICI discontinuation of 16 months. Among AI-patients, autoimmune hypothyroidism (16.5%), Sjogren's syndrome (13.6%), vitiligo (10.3%), sarcoidosis (10.0%), and psoriatic arthritis (9.6%) were the most common AIs, with 67.9% of patients indicating non-exacerbated and 32.1% of patients reporting exacerbated diseases. Within the group of outpatient ICI-patients - standing for an approximately representative group of patients treated in German skin cancer centres - about 41.5% of patients reported the presence of at least one persistent irAE (with 51.9%/35.5% of patients <12/≥12 months since therapy cessation). Arthralgia (16.3%), myalgia (13.6%), hypothyroidism (10.9%), vitiligo (9.5%), hypophysitis (8.2%), and xerostomia (8.2%) were the most common persistent irAEs. ICI-patients with persistent irAEs showed significantly and clinically relevantly reduced HRQoL scores compared to ICI-patients without persistent irAEs (subdivided by <12/≥12 months since ICI cessation: EQ-Index score: 0.767/0.752 versus 0.920/0.923, $p < 0.001/0.001$; EQ-VAS score: 52.2/52.0 versus 63.6/74.7, $p =/< 0.040/0.001$), which was consistent with the results of multiple linear regression analyses. Whereas ICI-patients with persistent irAEs had significantly reduced HRQoL compared with the normal population, ICI-patients without persistent irAEs indicated similar HRQoL compared to the normal population. Reductions in HRQoL, burden of autoimmune symptoms and burden of related therapies in the group of ICI-patients with persistent irAEs ≥12 months since ICI discontinuation were similar to those in patients with non-exacerbated AIs. ICI-patients with persistent irAEs received significantly less medications per autoimmune symptom than AI-patients. ICI-patients with persistent irAEs (≥12 months since ICI discontinuation) felt less adequately educated about possible side effects compared to ICI-patients without persistent irAEs.

For the publication, I assisted in the design of the questionnaires and in obtaining approval from the ethics committee. The recruitment of ICI-patients at the skin cancer centre of the LMU Hospital was mainly carried out by me; I was the contact person for the participating outpatient clinics. Recruitment through the support groups was done solely by me. Furthermore, I created the database, conducted the statistical analyses, and wrote the first draft of the manuscript (including tables and figures). Finally, I incorporated the review with support.

The publication showed that even ≥12 months after ICI cessation, about one third of patients still suffer from at least one persistent irAE, resulting in a significant reduction in HRQoL comparable to that caused by non-exacerbated AIs. Moreover, ICI-patients with persistent irAEs appear to be undertreated for their autoimmune symptoms and reveal a deficiency in patient education regarding potential persistent side effects.

2.2 Summary in German

Die Einführung der ICIs zur Behandlung bösartiger Erkrankungen hat die Onkologie revolutioniert. ICIs blockieren bestimmte Immun-Checkpoints und verstärken das körpereigene Immunsystem, so dass dieses Tumorzellen besser bekämpfen kann und teilweise dauerhafte Remissionen erreicht werden. ICIs wurden zunächst für die Behandlung des Melanoms eingesetzt. Mittlerweile finden ICIs Anwendung in einer zunehmenden Anzahl an Tumorentitäten – mit steigender Tendenz. Die Wirkungsmechanismen der ICIs ermöglichen ein bisher nicht gekanntes Ansprechen bei bestimmten Tumorentitäten, verursachen aber auch Nebenwirkungen, die sogenannten irAEs, die durch das überaktivierte Immunsystem ausgelöst werden und häufig AIs nachahmen. Obwohl die meisten irAEs durch die Unterbrechung oder die Beendigung der ICIs und/oder durch die Gabe von Immunsuppressiva reversibel sind, bleiben einige irAEs bestehen. In der Regel handelt es sich dabei um endokrinologische irAEs aber auch um einige kutane, rheumatologische oder neurologische irAEs. Bislang wurden nur sehr wenige Studien zu persistierenden irAEs nach ICI Beendigung sowie zu deren Auswirkungen auf das Leben der Krebsüberlebenden durchgeführt.

Die Publikation, auf der diese Dissertation basiert, untersuchte die Situation der mit ICIs behandelten Krebsüberlebenden bezüglich der Prävalenz persistierender irAEs sowie deren Auswirkungen auf die HRQoL der Patient*innen, die Belastung durch die autoimmunen Symptome sowie deren Therapien im Vergleich zu (korrespondierenden) AIs. Von April bis Oktober 2021 wurde eine multizentrische Fragebogen-basierte Querschnittsstudie in Ambulanzen (der Hautkrebszentren des LMU Klinikums in München, des Universitätsklinikums Schleswig-Holstein in Kiel und des Klinikums Bremerhaven-Reinkenheide in Bremerhaven sowie einer Abteilung für Innere Medizin des LMU Klinikums in München) und über Selbsthilfegruppen (für Krebspatient*innen und Patient*innen mit AIs) durchgeführt. ICI-Patient*innen (≥12 Wochen nach Absetzen der ICIs) und AI-Patient*innen wurden mit spezifischen ICI-/AI-Fragebögen untersucht. Diese enthielten sich überschneidende Fragen zur Demografie der Patient*innen, zur HRQoL (EQ-Index/VAS-Scores), zu anhaltenden (ICI-induzierten/nicht ICI-induzierten) autoimmunen Symptomen und deren Belastung sowie zu den damit verbundenen Therapien und deren Belastung. Von allen eingereichten Fragebögen (papierbasiert oder online) waren insgesamt 200 ICI-Fragebögen und 2705 AI-Fragebögen auswertbar und wurden in die statistischen Analysen (bestehend aus deskriptiv- und mathematisch-statistischen Methoden) einbezogen, die mit dem Programm SPSS Statistics (IBM®, Version 28.0) durchgeführt wurden.

Die meisten ICI-Patient*innen waren an einem Melanom (96,5%) in fortgeschrittenem Stadium (98,0%) erkrankt und zeigten ein vollständiges Ansprechen auf die Krebstherapien (67,5%). Pembrolizumab (41,0%), Nivolumab (39,5%) und Ipilimumab plus Nivolumab (29,5%) waren die am häufigsten angewendeten Therapien, mit (im Median) 16 Monaten nach Beendigung der ICI Therapie. Unter den AI-Patient*innen waren Autoimmunhypothyreose (16,5%), Sjögren-Syndrom (13,6%), Vitiligo (10,3%), Sarkoidose (10,0%) und Psoriasis-Arthritis (9,6%) die häufigsten AIs, wobei 67,9% der Patient*innen einen nicht-exazerbierten und 32,1% der Patient*innen einen exazerbierten Zustand angaben. In der Gruppe der ambulanten ICI-Patient*innen - die eine annähernd repräsentative Gruppe, der in deutschen Hautkrebszentren behandelten Patient*innen darstellt - berichteten etwa 41,5% der Patient*innen das Vorhandensein mindestens einer persistierenden irAE (bei 51,9%/35,5% der Patient*innen <12/≥12 Monate nach Therapiebeendigung). Die häufigsten persistierenden irAEs waren Arthralgie (16,3%), Myalgie (13,6%), Hypothyreose (10,9%), Vitiligo (9,5%), Hypophysitis (8,2%) und Xerostomie (8,2%). ICI-Patient*innen mit persistierenden irAEs wiesen im Vergleich zu ICI-Patient*innen ohne persistierende irAEs signifikant und klinisch relevant reduzierte HRQoL-Scores auf (unterteilt nach <12/≥12 Monaten seit ICI-Ende: EQ-Index-Score: 0,767/0,752 versus 0,920/0,923, $p < 0,001/0,001$; EQ-VAS-Score: 52,2/52,0 versus 63,6/74,7, $p =/< 0,040/0,001$). Dies war konsistent mit den Ergebnissen der multiplen linearen Regressionsanalysen. Während ICI-Patient*innen mit persistierenden irAEs im Vergleich zur Normalbevölkerung eine signifikant reduzierte HRQoL aufwiesen, hatten ICI-Patient*innen ohne persistierende irAEs eine ähnliche HRQoL wie die Normalbevölkerung. Die Reduktion der HRQoL, die Belastung durch die autoimmunen Symptome und die Belastung durch die damit verbundenen Therapien waren in der Gruppe der ICI-Patient*innen mit persistierenden irAEs ≥12 Monate nach Absetzen der ICIs ähnlich zu denen der Patient*innen mit nicht-exazerbierten AIs. ICI-Patient*innen mit persistierenden irAEs erhielten signifikant weniger Medikamente pro autoimmunem Symptom als AI-Patient*innen. ICI-Patient*innen mit persistierenden irAEs (≥12 Monate nach Absetzen der ICIs) fühlten sich im Vergleich zu ICI-Patient*innen ohne persistierende irAEs weniger gut über mögliche Nebenwirkungen aufgeklärt.

Zur Erstellung der Publikation half ich mit bei der Gestaltung der Fragebögen sowie bei der Einholung der Zustimmung durch die Ethikkommission. Die Rekrutierung der ICI-Patient*innen im Hautkrebszentrum des LMU Klinikums wurde hauptsächlich von mir durchgeführt; daneben war ich der Ansprechpartner der teilnehmenden Ambulanzen. Die Rekrutierung der Patient*innen über die Selbsthilfegruppen erfolgte allein durch mich. Des Weiteren erstellte ich die Datenbank, führte die statistischen Analysen durch

und schrieb den ersten Entwurf des Manuskripts (einschließlich Tabellen und Abbildungen). Mit Unterstützung wurde von mir das Review eingearbeitet.

Im Rahmen der Publikation konnte gezeigt werden, dass selbst ≥12 Monate nach dem Absetzen der ICIs etwa ein Drittel der Patient*innen an mindestens einer persistierenden irAE leidet. Dies führt zu einer signifikanten Verringerung der HRQoL, vergleichbar mit der durch nicht-exazerbierte AIs. Darüber hinaus scheinen die autoimmunen Symptome der ICI-Patient*innen mit persistierenden irAEs nicht ausreichend behandelt zu werden und es wurde ein Defizit in der Aufklärung der Patient*innen zu möglichen persistierenden Nebenwirkungen festgestellt.

3 Publication

The publication "Persistent immune-related adverse events after cessation of checkpoint inhibitor therapy: Prevalence and impact on patients' health-related quality of life" can be accessed by the following link:

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