Diagnostic and prognostic factors of metastatic melanoma: challenges and advances in modern therapy

Doctoral (Ph.D.) thesis

Melánia Pozsgai M.D.

Pécs

2025

Diagnostic and prognostic factors of metastatic melanoma: challenges and advances in modern therapy

Doctoral (Ph.D.) thesis

Melánia Pozsgai M.D.

Supervisor: Zsuzsanna Lengyel, M.D., Ph.D

Doctoral School of Clinical Medical Sciences

Doctoral School Leader: Prof. Lajos Bogár, M.D., Ph.D

Program Leader: Prof. András Vereczkei, M.D., Ph.D

Department of Dermatology, Venereology and Oncodermatology

University of Pécs, Medical School

Pécs

2025

2. Introduction

2.1 Melanoma epidemiology

Melanoma is a malignant tumor arising from melanocytes and represents one of the most aggressive and treatment-resistant skin cancers. It carries a high risk of metastasis and accounts for the majority of skin cancer-related deaths worldwide. According to the World Health Organization, more than 300,000 new cases are diagnosed globally each year, including an estimated 3,000 cases annually in Hungary. Although the global incidence of melanoma continues to rise, recent data suggest a declining trend among younger age groups.

2.2 Melanoma therapies

For many years, melanoma treatment relied on surgery, chemotherapy, and radiotherapy, but these approaches offered limited benefit in advanced disease. Advances in melanoma biology and tumor immunology have since enabled the development of more effective systemic therapies. Targeted therapies directed at oncogenic drivers particularly BRAF mutations led to the introduction of BRAF (vemurafenib, dabrafenib, encorafenib) and MEK inhibitors (trametinib, cobimetinib, binimetinib), which show strong initial efficacy but are often limited by acquired resistance.

Immune checkpoint inhibitors (ICIs) have revolutionized melanoma treatment, redefining patient outcomes. Agents targeting PD-1, CTLA-4, and PD-L1 markedly improve survival, and since the 2011 approval of ipilimumab, multiple ICIs have entered clinical practice. Landmark trials (KEYNOTE-006, CheckMate-067) demonstrated the survival benefits of pembrolizumab and nivolumab. ICIs are now standard in both metastatic and adjuvant settings (stage III and, since 2023, IIB/IIC), and emerging data support neoadjuvant immunotherapy as a promising next step. To further enhance efficacy, combination strategies such as nivolumab+ipilimumab or nivolumab + relatlimab (anti-LAG-3) target multiple checkpoints to overcome resistance.

2.3 PD-1 inhibitor side effects

Immune checkpoint inhibitors substantially improve survival but can trigger immune-related adverse events (irAEs) due to loss of peripheral tolerance. Cutaneous irAEs are the most common, frequently presenting with vitiligo, maculopapular rash, pruritus, lichenoid or psoriasiform eruptions, xerosis/xerostomia, and, less commonly, bullous pemphigoid or severe mucocutaneous reactions (SJS/TEN). Dermatologic irAEs may arise early (3–10 weeks),

although pigmentary changes such as vitiligo often occur later. A meta-analysis of 18,610 patients showed irAEs in 66% of ICI-treated individuals, with fatigue, pruritus, and diarrhea most frequently affected. Mechanistically, PD-1 blockade enhances T-cell activation and effector function but diminishes inhibitory signaling, enabling autoreactive responses against melanocytes, keratinocytes, and components of the dermo-epidermal junction.

2.4 Management of side effects

Most dermatologic irAEs are grade 1–2, self-limiting, and manageable with emollients, topical corticosteroids, and antihistamines. Severe reactions (grade ≥3) are uncommon but may necessitate systemic corticosteroids, temporary treatment interruption, or, rarely, permanent discontinuation. Recognition and grading follow CTCAE criteria. Cutaneous irAEs typically occur earlier than toxicities in other organs and are not dose-dependent. Early identification is essential, as skin reactions may significantly affect quality of life and treatment adherence. For severe phenotypes such as bullous pemphigoid, systemic corticosteroids remain first line. However, emerging evidence supports biologic therapies such as dupilumab and omalizumab for steroid-refractory or steroid-dependent cases, offering steroid-sparing benefits and improved tolerability.

2.5 Prognostic markers in melanoma treated with ICIs

Established clinicopathologic prognostic factors include Breslow thickness, ulceration, mitotic rate, sentinel lymph node status, and, in metastatic disease, LDH and S100 values. Additionally, demographic characteristics (age, sex) and ECOG performance status influence outcome. Despite advances with ICIs, validated predictive biomarkers of response remain elusive. TMB, PD-L1 expression, and tumor-infiltrating lymphocytes show potential but lack consistency between cohorts. Gene expression profiling tools such as Decision Dx-Melanoma (FDA Breakthrough Device) represent progress toward integrated genomic prognostication.

Cutaneous irAEs as prognostic markers

Accumulating evidence identifies cutaneous irAEs especially vitiligo, pruritus, and maculopapular rash as clinical surrogates of systemic immune activation. Multiple retrospective and prospective studies consistently demonstrate strong associations between dermatologic irAEs and longer PFS and OS in patients receiving PD-1 inhibitors. Sanlorenzo et al. first showed this in melanoma, with similar effects later confirmed in NSCLC. Importantly, the

prognostic value appears independent of PD-L1 expression, baseline characteristics, and prior therapies, suggesting that skin toxicity reflects heightened antitumor immunity.

2.7 Melanoma follow-up

Melanoma recurrence risk is highest in the first 2–3 years and rises sharply from stage IIB, as reflected in the AJCC 8th edition distinction between low-risk (IA–IIA) and high-risk (IIB–IV) disease. Historically, follow-up guidelines differed widely, and routine imaging for asymptomatic stage IIB patients was generally not recommended before 2016. The NCCN v3.2016 update marked a major shift by recommending CT/PET-CT ± brain MRI every 3–12 months for stage IIB–IV patients, followed by similar ESMO (2019) and European consensus (2022) guidance. These changes were driven by evidence showing that stage IIB recurrence rates resemble those of stage IIIA and that many metastases in this group are asymptomatic but radiologically detectable. With effective modern therapies including ICIs and BRAF/MEK inhibitors early detection of low-volume metastatic disease now confers clear survival benefit, supporting stage-stratified surveillance focused on IIB-IIIC patients, while early stages rely on clinical follow-up and patient self-examination. Large cohorts (e.g., Smith et al., 2022) confirm that over half of recurrences in stage IIB–IIIC are imaging-detected and frequently clinically silent. Ultrasound remains optimal for nodal assessment, CT/PET-CT for distant disease, and MRI for brain metastases. Imaging is also essential for evaluating immunotherapy-specific response patterns, including pseudoprogression. Overall, contemporary surveillance strategies emphasize risk-adapted imaging focused on high-risk stages, aligning with principles of tertiary prevention to detect recurrences earlier and preserve long-term survival and quality of life.

3. Objectives:

3.1 The Significance of Imaging Examinations in the Follow-up of Malignant Melanoma

- To evaluate the effectiveness and diagnostic yield of various imaging modalities particularly CT scans in detecting melanoma recurrences during follow-up across different disease stages, with special focus on the early (stage I-IIA) versus high-risk stages (stage IIB and above).

- To assess the timing, frequency, and mode of metastasis detection (e.g., patient self-examination, physician examination, ultrasound, CT, MRI) during melanoma surveillance, and to determine the value of each in contributing to early diagnosis of recurrence.

- To analyze the cost-effectiveness and clinical justification of routine imaging procedures, especially CT scans, in the follow-up of early-stage melanoma patients, taking into account recurrence rates, false-positive findings, and potential long-term radiation risks.

- To contribute to the optimization of melanoma follow-up protocols by identifying stage-specific imaging needs and highlighting the importance of patient education for self-examination, thereby promoting a more personalized and evidence-based surveillance strategy.

3.2 Cutaneous Side Effects of PD-1 Inhibitors: A Single-Center Retrospective Study

- To provide a comprehensive analysis of adverse events, with a primary focus on skin toxicities, in patients treated with PD-1 inhibitors for metastatic or adjuvant indications, and to investigate the prognostic significance of these events in relation to patient survival outcomes

- To analyze the incidence, clinical presentation, timing, and types of cutaneous adverse events associated with PD-1 inhibitor therapy (pembrolizumab and nivolumab) in stage III and IV melanoma patients, including inflammatory, pigmentary, and rare immune-mediated skin manifestations.

- To evaluate the correlation between the occurrence of cutaneous toxicities and oncologic outcomes, specifically progression-free survival and overall survival, thereby assessing the potential prognostic significance of dermatologic immune-related adverse events.

- To assess management strategies and therapeutic interventions for cAEs, aiming to balance effective symptom control with the continuity of immunotherapy.

4. Materials and Methods

At the Department of Dermatology, Venereology, and Oncodermatology of the University of Pécs, retrospective studies were conducted in two patient cohorts. Data were extracted from the MedSol database and anonymized prior to analysis.

4.1 CT Scans in the Follow-Up of Malignant Melanoma

4.1.1 Study Design and Patient Selection

The first retrospective cohort included patients with histologically confirmed melanoma diagnosed between 2001–2011. Exclusion criteria were: melanoma in situ, stage IV disease at diagnosis, unknown stage, and follow-up < 3 years. The melanoma database provided detailed clinicopathologic, staging, treatment, recurrence, and imaging data. The study began in December 2014.

4.1.2 Imaging and Follow-Up Protocol

Staging followed the AJCC 7th edition. Sentinel lymph node biopsy was performed for tumors > 0.75 mm, ulcerated, or with mitotic index >1/mm². High-risk disease was defined as stage IIB+ based on ESMO 2015. Between 2001–2011, institutional staging included chest/abdominal CT, head CT or MRI, and physical examination. Routine follow-up consisted of:

- Annual chest/abdominal CT and head CT/MRI
- Semiannual CXR, abdominal and nodal ultrasound
- Physical exams every 3 months (years 0–3), then every 6 months to year 10
  Patients were advised on self-skin examination.

4.1.3 Imaging Classification

CT findings were categorized as true-positive, false-positive, or true-negative. Detection modality (imaging vs. clinical) was assigned per patient without overlap. Incidental non-melanoma tumors were also recorded.

4.1.4 Statistical Analysis

Recurrence timing, detection modality, and survival trends were analyzed using Kaplan–Meier curves with log-rank tests ($p < 0.05$). CT, ultrasound, physician examination, and patient self-examination were evaluated separately. Analyses were performed using GraphPad Prism, and the study received IRB approval (AOK/2018/7356).

4.2 Cutaneous Side Effects of PD-1 Inhibitors

4.2.1 Study Design and Patient Selection

The second retrospective study included patients with stage III or IV melanoma treated with pembrolizumab or nivolumab between August 2015–May 2022. Exclusions: loss to follow-up, clinical trial participation, and anti–PD-1 + ipilimumab combination therapy.

4.2.2 Data Collection

Collected variables included demographics, treatment type/duration, onset and grade of cutaneous and non-cutaneous AEs, prior skin diseases, treatment of AEs, eosinophil counts (baseline and at AE onset), and dates of progression or death. AEs were graded using CTCAE v4.03, and treatment response was assessed via RECIST v1.1.

4.2.3 Statistical Analysis

PFS was measured from therapy initiation to progression; OS from initiation to death, with censoring at last follow-up when applicable. Kaplan Meier curves with log-rank tests were used for OS/PFS. Comparisons of AE onset and severity used the Mann–Whitney test. Covariates (age, sex, Breslow thickness, ulceration, LDH, ECOG, stage, line of therapy, comorbidities) were tested using chi-square or Fisher's exact tests. Cox regression evaluated their impact on OS/PFS. Analyses were conducted in R 3.5.1, GraphPad Prism v8, and Excel. IRB approval: AOK/2024/9913.

5. Results

5.1 CT scans in the follow-up of malignant melanoma

5.1.1 Patient Cohort and Baseline Characteristics

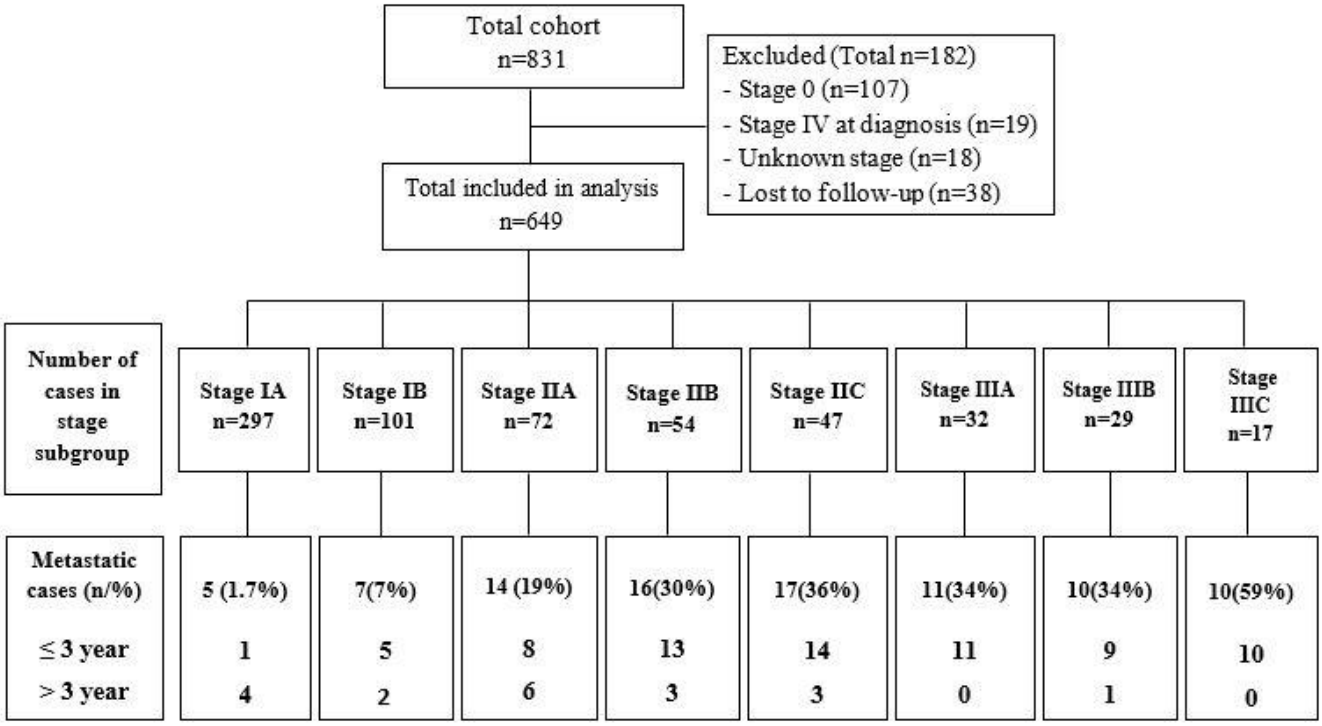
Between 2001 and 2011, 831 patients were diagnosed with melanoma. A total of 182 patients were excluded: 107 with melanoma in situ (stage 0), 19 with stage IV disease at diagnosis, 18 with insufficient histopathologic data, and 38 who were lost to follow-up within three years. Thus, the final study cohort consisted of 649 patients.

The analyzed cohort consisted of 339 women (52%) and 310 men (48%), with a mean age of 56.7 years (range: 16-95 years). More than half of the patients were diagnosed with stage I disease: 297 patients (46%) with stage IA and 101 patients (16%) with stage IB. The distribution for other stages was as follows: stage IIA – 72 patients (11%), stage IIB – 54 patients (8%), stage IIC – 47 patients (7%), and stage III – 78 patients (12%) (Figure 1). The median follow-up period was 5.3 years (range: 3-13 years).

5.1.2 Recurrence Rates and Timing by Stage

During follow-up, recurrences were detected in 90 patients (14%): 12 out of 398 (3%) among stage I, 47 out of 173 (27%) among stage II, and 31 out of 78 (40%) among stage III patients. The distribution of all cases and recurrences by stage is illustrated in Figure 1.

Figure 1. *Study population. The figure summarizes the characteristics of the patient cohort, including the number of excluded and analyzed cases at each stage, as well as the number of metastatic cases per stage. Percentages in the horizontal rows indicate the proportion of metastatic cases relative to the total number of cases within each stage subgroup*



.

5.1.3 Detection Modality of Early Recurrences

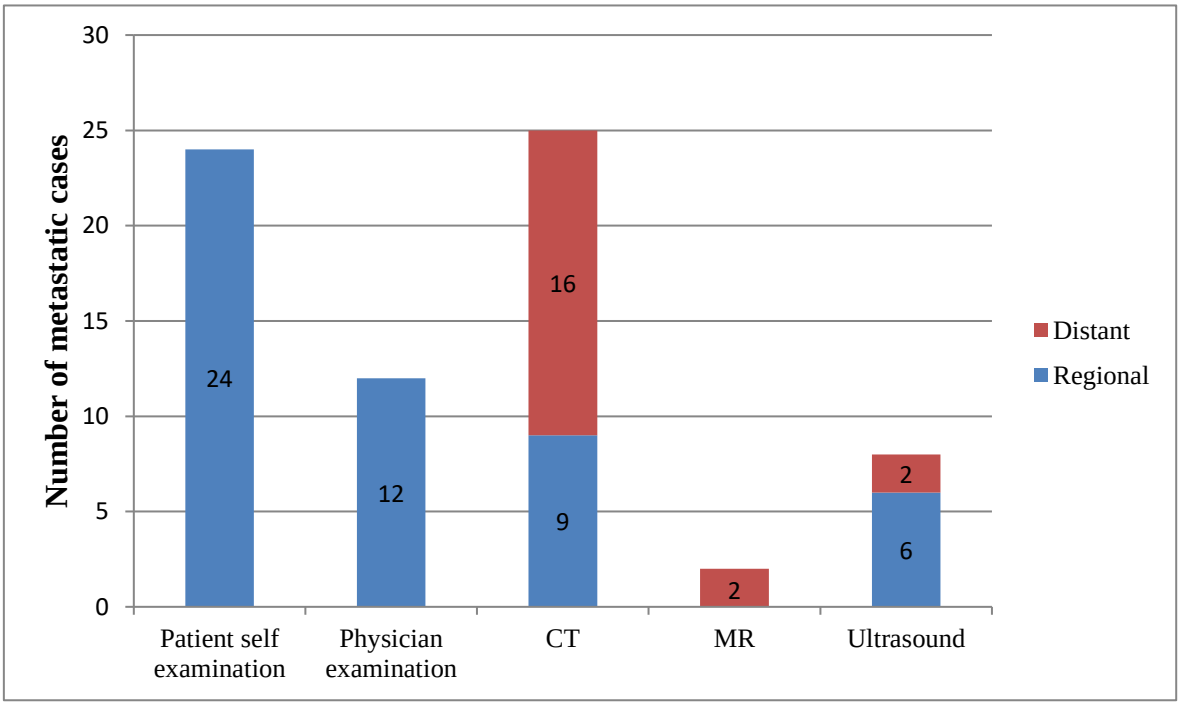
Of the 90 patients who developed metastases, 71 cases (79%) occurred within the first three years of follow-up: 40 cases in the first year, 23 in the second year, and 8 in the third year. Among these, 51 were regional recurrences including 21 nodal and 30 in-transit metastases and 20 were distant metastases. The most frequent sites of distant metastases during the first three years were the lungs (6 cases), followed by distant lymph nodes (4 cases), brain (3 cases), and liver (2 cases). In 5 cases, metastases involved multiple organ systems simultaneously.

With regard to detection methods used during the first three years:

- 24 metastases were initially recognized by patients themselves through self-examination.
- 12 cases were identified during routine physical examination.
- 35 cases were discovered through imaging, including 25 by CT, 8 by ultrasound, and 2 by MRI.

Thus, 49% of all metastases identified in the first three years were detected through imaging studies. Notably, CT alone accounted for 35% (25 cases) of these early recurrences. Of the CT-detected metastases, 64% (16 cases) were distant metastases and 36% (9 cases) were regional (Figure 2).

Figure 2. *Distribution of metastatic cases (n = 71) detected within the first three years of follow-up. CT identified 25 cases (35%), patient self-examination 24 cases (34%), physical examination 12 cases (17%), ultrasound 8 cases (11%), and MRI 2 cases (3%). Note: Cases reflect detections per modality; methods were not mutually exclusive.*



Importantly, all CT-detected distant metastases occurred despite negative imaging within the previous six months (abdominal ultrasound and chest X-ray). No parallel imaging was performed, so earlier detection by other modalities cannot be assessed. Prior studies, however, demonstrate the superior sensitivity of CT for pulmonary metastases: CT detects nodules < 5 mm, whereas chest X-ray identifies only ~50% of nodules 6–10 mm.

Regarding regional metastases detected by CT (n=9), all scans were performed before scheduled follow-up visits. Although patients were asymptomatic, subsequent examination revealed enlarged lymph nodes in five cases, indicating that half of the regional metastases would have remained clinically occult without imaging.

5.1.4 Late Recurrence After Three Years

Beyond the first three years, 19 additional recurrences were documented: 9 cases in year 4, 4 cases between years 5-6, and 6 cases after the sixth year.

5.1.5 Diagnostic Yield of Detection Method

We assessed the performance of different follow-up methods over time and across tumor stages. CT scans demonstrated the highest and most consistent detection rates across stages and throughout the follow-up period. Ultrasound proved particularly effective during the early years of surveillance, but no metastases were detected by this method beyond the fifth year, resulting in a prolonged plateau phase thereafter. Patient self-examinations and physician examinations likewise detected the majority of metastases within the first five years, after which their detection rates remained stable, resembling the long-term pattern observed with CT. Stage-specific differences were also evident: patients with stage IIIC disease showed the steepest decline within the first two years, reflecting early metastatic spread, whereas stage IIA patients exhibited the most gradual decline, with metastases detected as late as seven years after the initial diagnosis,

5.1.6 Incidental Detection of other Malignancies

In addition to melanoma recurrences, 21 patients (3%) were diagnosed with other non-cutaneous malignancies during the follow-up period. These included 7 renal, 5 central nervous system, 3 bladder, 3 prostate, 1 lung, 1 ovarian tumor, and 1 case of follicular lymphoma. The occurrence of these malignancies was uniformly distributed across melanoma stages. No seasonal variation was observed in the timing of metastasis detection.

5.1.7 CT Scan Utilization and Diagnostic Performance

Throughout the ten-year follow-up period, a total of 6.555 CT scans were performed. Of these, 3.633 CT scans (55%) were completed within the first three years, along with 707 brain MRIs. Among the CT scans performed during the first three years, 28 (0.8%) yielded true-positive results, while 39 (1.07%) were false-positive. On average, each patient underwent approximately five CT scans in the first three years (1-2 annually).

We further examined CT scan frequency and positivity according to melanoma stage:

- In stage IA, 1.739 CT scans (48% of total CTs) were performed, none of which identified metastatic disease.
- In stage II, 780 CTs were conducted, of which 14 (1.8%) detected metastases.
- In stage III, 449 CTs were performed, with 11 (2.4%) yielding positive findings

5.2 Cutaneous Side Effects of PD-1 Inhibitors

5.2.1 Patient Demographics and Treatment Characteristics

A cohort of 174 patients with advanced melanoma were enrolled in this analysis, consisting of 96 men and 78 women. All the patients in the study were of Caucasian ethnicity. The median age at initiation of anti-PD-1 therapy was 64 years. Among the cohort, 107 patients (61%) received pembrolizumab, while 67 patients (39%) received nivolumab. The median duration of anti-PD-1 treatment was 10 months, with a median of 11 infusions administered during this period.

Anti-PD-1 therapy was primarily administered as follows: 66 patients (38%) received it in the frontline setting, 38 patients (22%) in the second line, 16 patients (9%) in the third line, 4 patients in the fourth line, and 1 patient in the fifth line. Additionally, 48 cases involved the use of anti-PD-1 therapy as an adjuvant treatment, while 1 patient received it as a neoadjuvant therapy. At the end of the study, 33 patients were still undergoing anti-PD-1 treatment.

5.2.2 Frequency and Severity of Adverse Events

A total of 148 adverse events, both cutaneous and non-cutaneous, were observed in 96 (55%) patients, with 39 (41%) of these individuals experiencing more than one adverse event. The median onset time for any adverse event was 19 weeks following the initiation of anti-PD-1 infusion. Most adverse events (138; 93%) were graded as 1-2, with only 10 cases (7%) reaching grade 3-4 according to CTCAE criteria.

Treatment was interrupted in 74 (43%) cases because of disease progression, in 14 cases due to death and in 10 cases due to toxicity-related reasons. Among the latter, adverse events included nephritis (3 cases), colitis (1 case), hypophysitis (1 case), hypoadrenia (1 case), anemia (1 case), myopathy (1 case), and skin toxicity (2 cases).

A comprehensive overview of patient characteristics is provided in **Table 3.**

Table 3: *Patients characteristics. Abbreviations: cAE, cutaneous adverse event; NA, not applicable; N, number of subjects.*

Patient demographic characteristics	**Number of patients with cutaneous adverse event N=50**	**Number of patients without cutaneous adverse event N= 124**	**Total number of patients N=174**
Male	29	67	**96**
Female	21	57	**78**
Median age at anti-PD-1 initiation	65 (27-87)	64 (21-87)	**64 (21-87)**
Clinical characteristics			
Previous history of vitiligo	3	NA	**3**
Previous history of atopy or inflammatory disease	5	NA	**5**
Treatment characteristics, N*(%)*			
Pembrolizumab	28 (56%)	79 (64%)	**107 (61%)**
Nivolumab	22 (44%)	45 (36%)	**67 (39%)**
Median time of anti PD-1 treatment	14 (3-52) months	6 (1-46) months	**10 (1-52) months**
Median number of infusions	18 (3-68)	8 (1-61)	**11 (1-68)**
Cause of anti-PD-1 interruption, N*(%)*			
Progression	15 (30%)	59 (48%)	**74 (43%)**
Death	3 (6%)	11 (9%)	**14 (8%)**
Toxicity	1 (2%)	9 (7%)	**10 (6%)**
Anti-PD-1 line, N*(%)*			
First line	36 (72%)	90 (73%)	**126 (72%)**
Second line	10 (20%)	27 (22%)	**37 (21%)**
Third line	4 (8%)	5 (4%)	**9 (5%)**
Fourth line	0	1 (0,08%)	**1 (0,6%)**
Fifth line	0	1 (0,8%)	**1 (0,6%)**
adjuvant	11 (22%)	37 (30%)	**48 (28%)**
neoadjuvant	0	1 (0,8%)	**1 (0,6%)**
Elevated eosinophil count during anti PD-1, N*(%)*	9 (18%)	NA	**9 (5%)**

Non cutaneous adverse events under anti PD-1, N*(%)*	**Number of events among patients with cutaneous adverse event N=30**	**Number of events among patients without cutaneous adverse event N=52**	**Total number of non-cutaneous adverse events N=82**
Thyroiditis	9 (30%)	16 (31%)	**25 (30%)**
Fatigue	12 (40%)	6 (12%)	**18 (22%)**
Pneumonitis	3 (10%)	7 (13%)	**10 (12%)**
Hypophisitis	1 (3%)	1 (2%)	**2 (2%)**
Other toxicity (colitis, reflux, eye dryness, nephritis, anemia, pancreatitis, diabetes, lower platelet count, polymyalgia rheumatica)	5 (17%)	22 (42%)	**27 (33%)**
Grade 1	17 (56%)	18 (35%)	**35 (43%)**
Grade 2	12 (40%)	27 (52%)	**39 (48%)**
Grade 3	1 (3%)	6 (11%)	**7 (8%)**
Grade 4	0	1 (2%)	**1 (1%)**

5.2.3 Characteristics of cutaneous AEs

Cutaneous adverse events occurred in 50 patients (29%), with a total of 66 cAEs, evenly distributed between pembrolizumab (n=33) and nivolumab (n=33) (Table 4). Among affected patients, 35 developed one cAE, 13 had two, and two patients presented with ≥3 concurrent events. A minority had pre-existing skin disease (vitiligo: 3 patients; atopy/inflammatory dermatoses: 5 patients). In 26 cases, cAEs occurred together with non-cutaneous toxicities.

The most frequent cAEs were vitiligo (18; 27%), pruritus (14; 21%), and maculopapular rash (14; 21%). Less common manifestations included xerostomia (8), lichenoid rash (4), acneiform rash (2), psoriasis progression (1), bullous pemphigoid (1), Grover's disease (1), erythema multiforme–like rash (1), alopecia areata (1), and eosinophilic folliculitis (1).

Most events were mild: 28 grade 1, 36 grade 2, and only 2 grade 3 (bullous pemphigoid and erythema multiforme-like rash), both under nivolumab. No grade 4 events occurred, and no treatments were permanently discontinued. cAEs appeared at a median of 22 weeks after therapy initiation.

5.2.4 Classification of Specific Cutaneous Reactions

5.2.4.1 Inflammatory Skin Reactions

Maculopapular rash occurred in 14 patients, with a median onset of 7.5 infusions and 23.5 weeks. All were grade 1–2 and resolved within approximately 7 weeks using topical corticosteroids ± antihistamines. Treatment was briefly interrupted in two cases. Concomitant AEs appeared in 7 patients.

Lichenoid rash was observed in 4 patients, including oral or genital involvement. Histology showed a band-like interface dermatitis. Median onset was 7 infusions and 17.5 weeks. All cases responded to topical corticosteroids without therapy modification. Two patients developed thyroiditis and two showed eosinophilia.

Psoriasiform rash: One patient experienced psoriasis exacerbation at week 25 after 8 infusions, successfully treated with topical steroids.

Pruritus was reported in 14 patients, with 5 isolated cases. Median onset was 7 infusions and 18 weeks. Most were grade 2 (n=11). Managed with moisturizers, antihistamines, and topical steroids; complete resolution occurred in 10 patients.

Other Dermatological Manifestations

Vitiligo: Observed in 18 patients (16 de novo; 2 flare-ups). Median onset was 28 weeks and 8 infusions. Lesions commonly involved: face (9), hands (8), forearms (7), trunk (6), neck (4), chest and legs (3 each). One patient developed total hair depigmentation after 44 weeks. Vitiligo co-occurred with other cAEs in 4 patients, and with systemic AEs in 10 patients. Severity was grade 1 (n=8) and grade 2 (n=10). Eosinophilia was detected in four cases (Figure 4. c).

Xerostomia: Eight cases developed after a median of 15 weeks and 4 infusions. Five occurred with another cAE. Managed with mucosal lubricants; autoimmune serology was negative in all four tested patients.

Bullous Eruptions: One patient developed bullous pemphigoid after the second nivolumab infusion. The eruption required systemic corticosteroids and recurred after steroid taper and nivolumab re-challenge. Nivolumab was discontinued, and pembrolizumab was initiated with intermittent mild blistering controlled by low-dose oral steroids.

5.2.4.2 Rare dermatological toxicities

Morbus Grover: One case occurred after 69 weeks, presenting with pruritic papules on the trunk and arms. It resolved after 6 weeks of topical steroids. Fatigue and hypothyroidism were also present.

Acneiform rash: Two patients developed grade 1-2 acneiform eruptions after 2–4 infusions (~8 weeks). Both resolved spontaneously within months.

Erythema multiforme–like rash: One grade 3 case appeared after the first infusion, confirmed histologically. Treatment was paused for two months and the eruption resolved with topical/systemic steroids. Therapy was restarted; the patient di ed 8 months later.

Alopecia areata: One patient developed alopecia areata after 88 weeks and 20 infusions, with regrowth after 3.5 months of topical therapy.

Eosinophilic folliculitis: One case occurred after 81 weeks, confirmed histologically, in a patient who also had four other cAEs (vitiligo, maculopapular rash, pruritus, alopecia areata) and hypothyroidism.

5.2.5 Non-Cutaneous Immune-Related Adverse Events

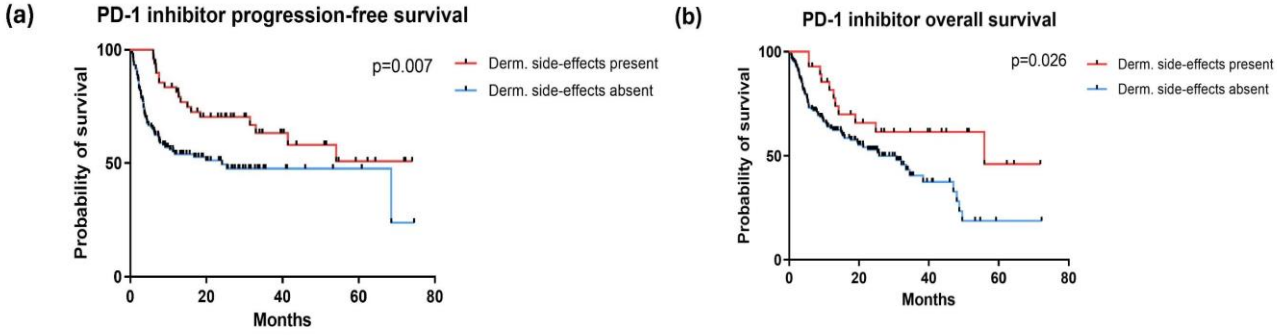
A total of 82 non-cutaneous irAEs occurred in 72 patients; 46 had only non-cAEs, while 26 experienced both cutaneous and non-cutaneous toxicities. Most patients (83%) developed a single non-cAE, whereas 12 (17%) had two events. Pembrolizumab was given to 47 patients (65%), nivolumab to 25 (35%), with a median onset of 4.2 months.
The most frequent toxicities were thyroiditis (25; 30%), fatigue (18; 22%), pneumonitis (10; 12%), followed by colitis (5) and nephritis (3). Less common events included hypophysitis, pancreatitis, myopathy, polymyalgia rheumatica, adrenal insufficiency, anemia, diabetes, neuropathy, encephalitis, thrombocytopenia, and ocular dryness.

5.2.6 Survival Outcomes in Relation to Skin Toxicity

Patients who developed cAEs during PD-1 inhibitor therapy had significantly improved PFS ($P = 0.007$) and OS ($P = 0.026$) compared with patients without skin toxicity (Figure 7a–b). At 1 year, PFS was 81% in the cAE group versus 56% in the total cohort, while OS was 82% versus 62%, respectively. Median PFS and OS were significantly higher in the cAE group

compared to those without such events (median PFS 26 months vs. 9 months, $P<0.0001$; median OS 26 months vs. 11 months, $P<0.0001$).

Figure 7. *Kaplan-Meier curves of (a) progression-free survival and (b) overall survival in melanoma patients treated with anti-PD-1 therapy compared by present and absent of dermatological side effects*.



Among patients who developed cAEs, 31 (62%) were alive at study end. The cAE group also demonstrated higher response rates, with 60% achieving complete (17/50) or partial responses (7/50), and 6 maintaining stable disease.

Subset analysis showed better OS (*P*=0.0008) and PFS *(P*<0.001*)* in vitiligo patients compared to non-vitiligo and non-cAEs cases (Figure 9). A similar trend was observed in the inflammatory group (*P*=0.06), which included maculopapular rash, lichenoid rash, and psoriasis. However, no significant results were found when examining the maculopapular group separately.

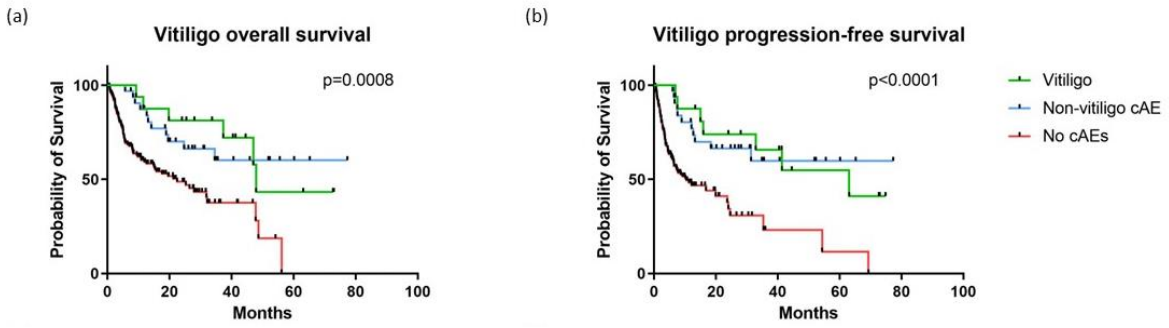


Figure 9. *Kaplan–Meier curves of (a) overall survival and (b) progression-free survival comparing the presence and absence of dermatological side effects, including vitiligo versus non-vitiligo cases.*

We conducted a detailed analysis comparing the cAEs and non-cAEs groups with respect to prognostic factors, including the patient age, gender; primary tumor's Breslow thickness, ulceration; LDH levels, ECOG status, comorbidities, tumor stage and line of therapy. This analysis aimed to rule out any independent effects of therapy success or life expectancy. No significant differences were identified between the subgroups, further supporting our findings of improved OS and PFS outcomes in the cAEs group compared to the non-cAEs group. Furthermore, a multivariate analysis involving major prognostic factors indicated that while ECOG status ≥ 1 was associated with a significant negative effect on both OS and PFS, the presence of cAEs was in turn associated with a significant positive effect (longer survival periods in both OS and PFS).

When analyzing adjuvant and metastatic subgroups separately, metastatic patients with cAEs showed significantly improved OS and PFS compared with those without cAEs. In the adjuvant cohort, a similar favorable trend was observed, although interpretation is limited by shorter follow-up and smaller sample size (Figure 10a-b). There were no significant differences in the incidence or severity of cutaneous versus non-cutaneous AEs between adjuvant and metastatic patients (Figure 10 c–e).

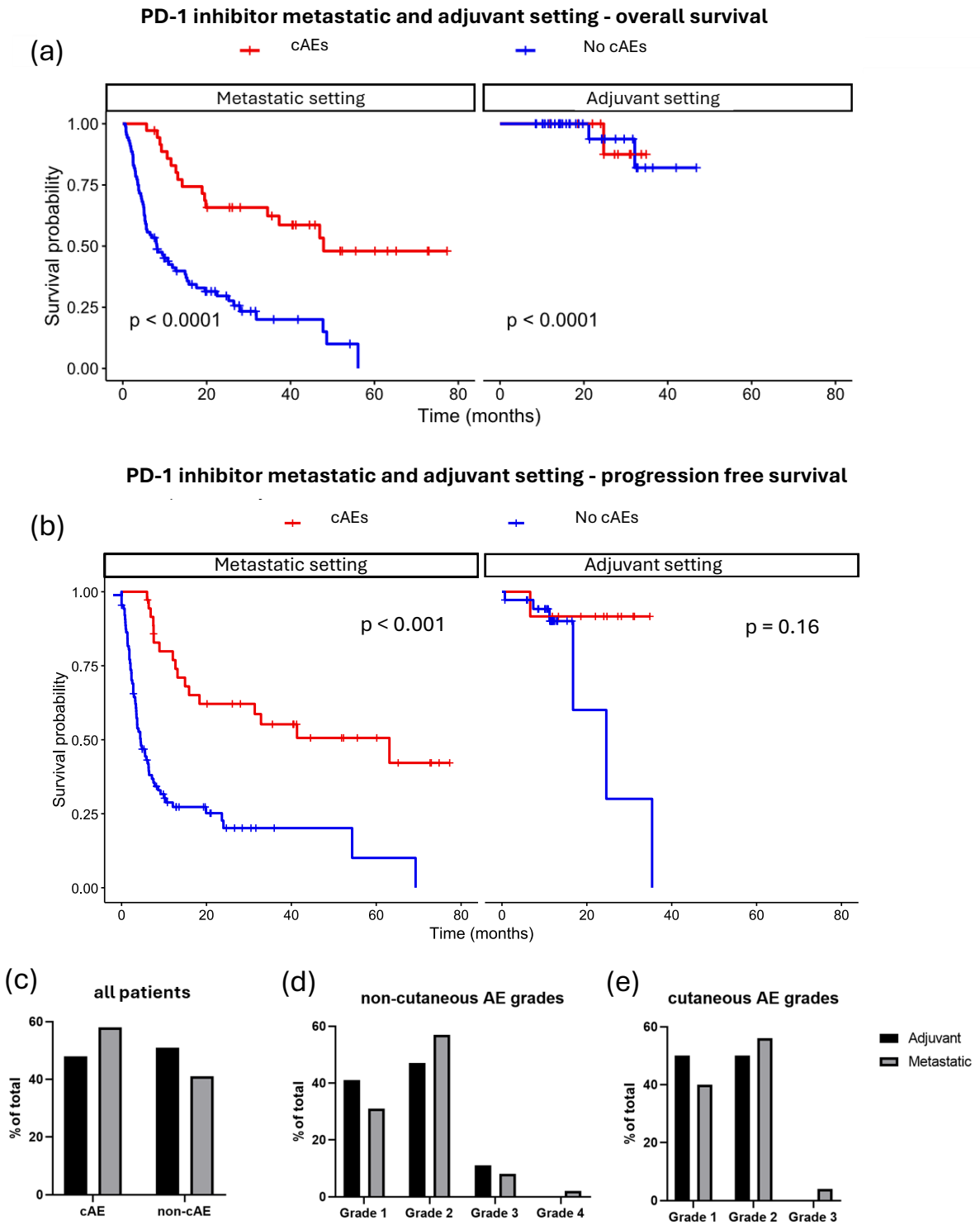


Figure 10. *(a-b) Kaplan Meier curves showing the OS and PFS of metastatic and adjuvant setting patients comparing the presence and absence of dermatological side effects. (c-e) Bar charts showing the ratio of metastatic and adjuvant setting patients. (c) All patients with cutaneous and non-cutaneous side effects. (d) Non-cutaneous side effects categorized by grade. (e) Cutaneous side effects, categorized by grade. Fisher's exact test on count data between adjuvant and metastatic groups is not significant in either comparison.*

6. Discussion

Our institutional protocol before 2013 required annual CT and semi-annual ultrasound and chest X-ray for all melanoma patients, allowing assessment of stage-independent intensified CT surveillance, particularly during the first three years when most recurrences occur. In our cohort, 79% of all metastases were detected within this period, predominantly as internal, imaging-detectable lesions. Recurrence risk was strongly stage-dependent: 3% (stage I), 19% (IIA), and 30% (IIB), supporting current guidelines that classify stage IIB as high risk.

Among detection methods, CT was the most effective (35% of recurrences), outperforming ultrasound (11%), physician examination (17%), and patient self-detection (34%). CT yield was minimal in early-stage disease (IA–IIA), aligning with evidence that routine imaging in low-risk patients has limited diagnostic value and contributes to radiation exposure and costs. PET/CT shows superior performance for distant metastases, and MRI remains the preferred modality for brain metastases. These findings support guideline recommendations favoring stage-adapted imaging, with CT/PET CT every 3–12 months for stage IIB–IV and clinical follow-up for earlier stages. Patient education remains essential, as 34% of recurrences were self-detected.

Early detection remains critical in the era of effective systemic therapies, as lower tumor burden at treatment initiation significantly improves outcomes with targeted therapy and PD-1 inhibitors. In our immunotherapy cohort, 29% of patients developed cutaneous immune-related adverse events (cAEs), mostly mild and comparable between pembrolizumab and nivolumab.

A key finding was that cAEs were strongly associated with improved PFS and OS, independent of known prognostic factors. Vitiligo showed the most pronounced association with survival, consistent with multiple large studies and meta-analyses indicating ~50% reduced mortality risk among patients who develop cutaneous irAEs. Mechanistically, this is likely driven by robust systemic immune activation and epitope spreading, as supported by histopathology and translational research demonstrating CD8+ T-cell infiltration and IFN-γ–mediated pathways.

Other inflammatory cAEs maculopapular, lichenoid, and psoriasiform eruptions also favored better outcomes, though to a lesser extent. Most cAEs were manageable with topical therapy, and permanent discontinuation of PD-1 inhibitors was rarely required, consistent with international irAE management guidelines.

Cutaneous toxicity incidence and severity were similar in adjuvant and metastatic patients, indicating that cAEs reflect PD-1 blockade's intrinsic immunologic effects rather than tumor load. While prognostic associations were strongest in metastatic disease, an emerging positive trend was also observed in the adjuvant cohort.

These findings highlight the importance of integrating dermatologic evaluation into routine oncologic follow-up, as cAEs provide both clinical and prognostic information. The appearance of vitiligo or other cAEs may indicate effective immune activation and could influence decisions regarding treatment monitoring or surveillance intensity.

Limitations include the retrospective, single-center design and the predominantly Caucasian population, suggesting a need for larger prospective studies across diverse groups. Future efforts should focus on validating cAEs as prognostic markers, integrating biomarkers such as ctDNA and gene expression profiling for better risk stratification, and optimizing imaging intervals to balance early detection with cost, radiation exposure, and patient burden.

In summary, our findings support a risk-adapted melanoma surveillance strategy:

- Routine imaging is not justified for stage IA–IIA patients.
- Stage IIB+ patients benefit from structured CT/PET-CT surveillance, especially during the first three years.
- MRI is preferred for brain imaging; CT or PET-CT for systemic metastases.
- Dermatologic monitoring and patient self-examination are essential components of effective follow-up.
- Cutaneous adverse events during PD-1 inhibitor therapy serve as clinically meaningful markers of systemic antitumor activity, reinforcing their relevance in personalized melanoma care.

7. Summary

The management of melanoma increasingly relies on two interconnected pillars: modern imaging-based surveillance and immunotherapy. While CT and PET/CT enable the early detection of asymptomatic metastases, cutaneous adverse events emerging during PD-1 inhibitor therapy, such as vitiligo or inflammatory rashes, have proven to be not only common but also positive prognostic markers of treatment response. This link underscores the importance of integrated follow-up strategies where dermatologic monitoring complements radiologic surveillance. Recognizing cAEs as indicators of effective systemic immune activation can help guide imaging intervals and personalize patient care.

Novel findings and contributions:

• In our large single-center melanoma cohort (n=649; median follow-up 5.3 years), CT had negligible diagnostic yield in stages IA–IIA (e.g., stage IA: 0/1,739 CTs positive) but showed clear value from stage IIB upward, directly supporting risk-adapted imaging. These findings prompted revision of our institutional protocol and anticipated the 2016 NCCN recommendation to begin routine imaging at stage IIB.

• Comparing detection methods, imaging especially CT accounted for 35% of early recurrences, while patient self-examination contributed 34%, underscoring the combined importance of imaging and patient education.

• Our cohort of 174 anti–PD-1–treated patients was among the larger single-center datasets at the time, allowing detailed characterization of cAE phenotypes, onset, severity, and rare entities (e.g., Grover's disease, EM-like rash, eosinophilic folliculitis).

• Development of cAEs particularly vitiligo was associated with significantly improved PFS and OS, independent of confounders. Multivariable analyses confirmed cAEs as an independent favorable prognostic factor, while ECOG ≥1 predicted worse outcomes.

• cAE incidence and severity were similar in adjuvant and metastatic settings. Survival benefit was clear in metastatic patients and an emerging trend in adjuvant disease. This represents one of the first direct comparisons of PD-1 toxicities across indications, with only the recent study by Rauwerdink et al. (2024) providing similar data.

8. Acknowledgements

These studies were conducted at the Department of Dermatology, Venereology and Oncodermatology, University of Pécs, Medical School.

I thank my program leader, Professor András Vereczkei, for the opportunity to pursue my Ph.D. studies.

I am especially grateful to my project leader, Zsuzsanna Lengyel, MD, PhD, whose continuous guidance, expertise, and support from my undergraduate years to this thesis have been invaluable. I also thank Professor Rolland Gyulai for his consistent support and helpful guidance, particularly regarding my publications.

I acknowledge Dr. Péter Oláh for his assistance with statistical analyses, and Beáta Gyurita and Andrea Kiss for their essential help in data collection. Finally, I thank my family for their patience, understanding, and unwavering support throughout my academic journey.

10. List of Publications

Publications related to the present dissertation:

Pozsgai M, Németh K, Oláh P, Gyulai R, Lengyel Z. The significance of imaging examinations during follow-up for malignant melanoma. ***Eur J Dermatol***. 2021;31(3):357–363. doi:10.1684/ejd.2021.4054. PMID: 34309521. (**IF: 2.8**)

Pozsgai M, Sebastian UF-R, Oláh P, Németh V, Gyulai R, Lengyel Z. Cutaneous side effects of PD-1 inhibitors: a single-center retrospective study. ***Int J Dermatol***. 2025. doi:10.1111/ijd.17683. (**IF: 3.5**)

Publications not related to the present dissertation:

Pozsgai M, Oláh P, Battyáni Z, Kádár Z, Gyulai R, Lengyel Z. Tapasztalataink célzott gyógyszeres kezelésekkel metasztatikus melanomában. *Bőrgyógyászati és Venerológiai Szemle*. 2018;94(3):155–161.

Lengyel Z, Pozsgai M, Kádár Z, Durkot P, Horváth Z, Gyömörei C, Gyulai R. Újdonságok a ritka bőrtumorok ellátásában*Bőrgyógyászati és Venerológiai Szemle*. 2020;96(2):64–72.

Pozsgai M, Gyulai R, Gyömörei C, Lengyel Z. Cutan T-sejtes lymphomák bőrre irányuló kezelése (skin directed treatment) egy eset kapcsán. *Bőrgyógyászati és Venerológiai Szemle*. 2020;96(5):212–218.

Lengyel Z, Pozsgai M, Szebényi J, Oláh P, Battyáni Z. Fényvédőkészítmények napjainkban, amit érdemes tudni. *Bőrgyógyászati és Venerológiai Szemle*. 2023;99(3):175–181.

Németh C, Pozsgai M, Gyulai R, Lengyel Z. Protrusions within a pink-yellow plaque. *Dermatol Pract Concept*. 2022;12(1):e2022012. doi:10.5826/dpc.1201a12. PMID: 35223157; PMCID: PMC8824636.

Schneider C, Pozsgai M, Németh C, Battyáni Z, Lengyel Z. A healthy pregnancy during treatment of metastatic melanoma with immune checkpoint inhibitors: a case report. ***J Clin Med.*** 2025;14 (23):8591. (**IF**: **2.9**)