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CUTANEOUS MELANOMA. CURRENT DIAGNOSTIC AND THERAPEUTIC GUIDELINES WITH COMPARISON OF POLISH AND INTERNATIONAL CLINICAL PRACTICE AND FUTURE PERSPECTIVES

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ABSTRACT

Research objectives: Cutaneous melanoma is one of the most aggressive skin malignancies, characterized by a high potential for metastasis and a steadily increasing global incidence. While early-stage disease is associated with high cure rates, advanced melanoma has historically carried a poor prognosis, which has driven rapid advancements in both diagnostic technologies and systemic therapeutic strategies over the last decade.
Aim: This narrative review aims to synthesize current international diagnostic and therapeutic guidelines (ESMO, NCCN, ASCO) and compare them with Polish clinical practice (PTOK), focusing on recent shifts in surgical management, the role of adjuvant therapies, and future perspectives in personalized medicine and artificial intelligence.
Material and methods: The study is a narrative review based on the analysis of 21 recent peer-reviewed sources, including randomized controlled trials (RCTs), large-scale multicenter real-world studies from Poland, and the latest 2024 Clinical Practice Guidelines from the European Society for Medical Oncology and the National Comprehensive Cancer Network
Key findings: International standards now emphasize a significant de-escalation of radical surgery, specifically recommending the omission of completion lymph node dissection (CLND) following a positive sentinel lymph node biopsy (SLNB) in favor of active ultrasound surveillance. Adjuvant systemic therapies including anti-PD-1 immunotherapy and targeted BRAF/MEK inhibitors have become the standard of care for high-risk patients, significantly improving relapse-free survival. Real-world data from Poland demonstrate a rapid alignment with these global trends, although challenges persist, as Polish patients are often diagnosed at more advanced stages, with a mean Breslow thickness of approximately 2.0 mm compared to <1.0 mm in Europe. Additionally, emerging deep learning architectures are showing outstanding potential, with diagnostic accuracies for melanoma detection exceeding 95%.
Conclusions: Successful melanoma management requires a multidisciplinary approach and strict adherence to evidence-based international guidelines. The transition to early systemic adjuvant therapy allows for the safe de-escalation of surgical interventions without worsening patient prognosis. Future management will increasingly rely on personalized medicine through molecular biomarkers, mRNA neoantigen vaccines, and the clinical integration of artificial intelligence to improve early detection and treatment planning.

KEYWORDS

Melanoma, ESMO Guidelines, Adjuvant Therapy, Immunotherapy, Targeted Therapy, Sentinel Lymph Node Biopsy, Poland

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1. Introduction

Melanoma is a highly aggressive and complex malignant tumour. Its cells (melanocytes) arise from the neural crest and have high phenotypic plasticity; as pigment-producing cells, they are able to spread to different parts of the body and invade through the lymphatic system and the blood vessels (Al Zegair et al., n.d.-a; Caraviello et al., 2025a; Matkowski et al., 2025). Melanoma is not the most common skin tumour and represents only 1% to 4% of cutaneous neoplasms, but it is responsible for 75–80% of associated deaths (Al Zegair et al., n.d.-a; Matkowski et al., 2025; Rutkowski et al., n.d.-a). The incidence of melanoma has been increasing over the last few decades in fair-skinned populations, a trend that has roughly doubled every 10 years. Looking forward, global melanoma incidence is expected to increase by more than 50% in less than 20 years, from approximately 370,000 new cases in 2018 to more than 510,000 new cases and 90,000 deaths worldwide by 2040(Caraviello et al., 2025b; Sorino et al., 2024; Ziętek et al., 2022).

Skin diseases are increasing rapidly and their incidence nearly tripled in the last three decades. Over 3800 new cases of skin diseases are diagnosed every year in Poland(Rutkowski et al., n.d.-b). This increased risk for skin diseases is caused by both long- and short-term exposure to ultraviolet (UV) radiation from sun and tanning beds. Large numbers of fair-skinned individuals (Fitzpatrick types I and II) are permanently or

temporarily moving to areas with high solar radiation(Niemczyk et al., 2024; Rutkowski et al., n.d.-b; Sorino et al., 2024). UV-B (280-315 nm) is directly causing DNA mutations while UV-A (315-400 nm) is causing secondary damage to skin cells through the production of reactive oxygen species (ROS) and by induction of growth factors(Matkowski et al., 2025; Sorino et al., 2024).

Melanoma is a serious form of skin cancer that arises from pigment cells, also known as melanocytes. These mutations in the somatic cells of the skin occur over a long period of time in a stepwise fashion and lead to the transformation of normal melanocytes to malignant melanoma cells. Approximately 40% to 60% of melanomas are caused by one of these mutations in the BRAF gene(Al Zegair et al., n.d.-b; Kuchnicka et al., 2022; Rutkowski et al., n.d.-b). The majority of these mutations are the substitution of glutamic acid for valine at codon 600 (V600E BRAF) that results in constitutively active MAPK signaling pathway, which promotes cell survival and proliferation. Additional mutations include those that activate RAS, such as mutations in NRAS (15%–20%) and NF1 oncogenes. Other genes are inactivated in melanoma including CDKN2A and PTEN that act as tumor suppressors (Rutkowski et al., n.d.-b; Ziętek et al., 2025).

Although progress has been made in the development of new treatments for melanoma, the treatment outcome for most patients still depends largely on the pathologic stage at the time of diagnosis. Thin melanomas (Stage 0-II) detected early in the course of the disease are cured greater than 95% to 99%(Amaral et al., 2025). On the other hand, patients with metastatic melanoma have historically had a poor prognosis, with 5-year survival rates less than 10% before the modern era. However, over the last 15 years, there has been a paradigm shift in the management of patients with metastatic melanoma, transforming experimental therapies with poor outcomes to safe and effective therapies. The release of checkpoint inhibitors, including PD-1, CTLA-4, and LAG-3 blockade, and BRAF/MEK targeted therapy for the BRAFV600 mutant population, have transformed metastatic melanoma from an acute fatal disease to a chronic condition that can be managed in a significant portion of patients with this disease(Al Zegair et al., n.d.-b; Amaral et al., 2025).

There is significant “implementation gap” between guidelines and reality in diagnostics and treatment of children with melanoma in Polish reference centers where this disease is treated in clinical practice. Data available so far indicated that Polish children are diagnosed with more advanced primary tumors compared to children in Western Europe. Mean Breslow thickness was 2.0 mm versus <1.0 mm in Western Europe. Information how treatment strategies widely used worldwide, such as de-escalation of treatment for regional lymph nodes and early start of adjuvant therapy are actually applied in our center is also of utmost importance(Amaral et al., 2025).

The aim of this study is to present an overview of current international diagnostic and therapeutic recommendations and their implementation in clinical practice in Poland. Guidelines from the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) will be compared with current recommendations of the Polish Society of Clinical Oncology (PTOK)(Amaral et al., 2025; Rutkowski et al., n.d.-b; Swetter et al., 2024). The implementation of these recommendations in real world settings will be presented based on data obtained from the largest Polish oncological centers, including the Maria Skłodowska-Curie National Research Institute of Oncology and the Lower Silesian Oncology Center. The article will also discuss challenges in management of cancer patients and their prospects for treatment with the use of artificial intelligence, personalized mRNA neoantigen vaccines and new molecular biomarkers(Al Zegair et al., n.d.-b; Amaral et al., 2025).

2. Research materials and methods

This study is a scientific narrative review paper on qualitative data synthesis of evidence-based clinical data and current management practices with worldwide references issued in the last five years.

2.1. Data Collection and Analysis

A comprehensive literature search of several databases such as PubMed, Google Scholar and Science Direct was performed. A focus was placed on locating clinical relevant literature from the past five years (2020-2025), as well as referencing classic studies relevant in today’s medical era, in order to become familiar with historic staging manuals and notable studies that describe survival goals(Al Zegair et al., n.d.-b; Amaral et al., 2025; Wolchok et al., 2025).

A comprehensive literature search was conducted on various databases utilizing a combination of controlled vocabulary and keywords. The following terms were used: melanoma, cutaneous melanoma, immunotherapy, chemotherapy, metastasis, targeted therapy, artificial intelligence, dermoscopy, melanoma

diagnosis, melanoma treatment, BRAF mutation, survival, neoadjuvant therapy, adjuvant therapy, PD-1 inhibitors, CTLA-4, LAG-3 and melanoma biomarkers including the disease melanoma.

Inclusion criteria were strictly defined to prioritize:

1. Mechanism driven experimental studies aiming to better understand immune therapy; AUPRES study investigating the prognostic impact of three genes (CD8A, PDCD1, HLA-DQB1), future exploration of single-cell analysis(Amaral et al., 2025; Sorino et al., 2024).

2. International current recommendations (ESMO 2024, NCCN 2024/2025, ASCO 2023)(Amaral et al., 2025; Rutkowski et al., n.d.-b; Swetter et al., 2024).

3. Meta-analyses and systematic reviews on prognostic factors (sarcopenia and/or tumor mutational burden etc.) and reviews on AI accuracy for cancer diagnosis(Naseri & Safaei, 2025a; Surov et al., 2022).

4. Real-world evidence (RWE) and multicenter studies from Poland - results from centers: Maria Skłodowska-Curie National Research Institute of Oncology (Warsaw, Cracow, Gliwice branches), Lower Silesian Oncology, Pulmonology and Hematology Center (DCO Wrocław)(Placzke et al., 2023; Wysocki et al., 2024; Ziętek et al., 2023).

Articles have been selected for this supplement that describe clinical situations and management strategies that represent a paradigm shift in the management of melanoma, such as the potential for the de-escalation of completion retroperitoneal lymph node dissection, and the potential expansion of indications for adjuvant chemotherapy for Stage I patients to include patients with Stage IIB and/or IIC melanoma. Emphasis has also been placed on papers and presentations based on large patient numbers, long-term follow-up, and in some cases 7-year and 10-year updated results. These articles are intended to incorporate new findings into current national and international treatment algorithms(Amaral et al., 2025; Long et al., 2024; Wolchok et al., 2025).

2.2. Statistical Analysis

This is a narrative review and therefore a qualitative data synthesis technique was used to allow for the comparison of study outcomes. No meta-analysis was performed, but reference was made to results of existing meta-analyses found in the literature regarding sarcopenia and the accuracy of artificial intelligence (AI) in tumour diagnosis(Naseri & Safaei, 2025a; Surov et al., 2022).

Analysis of effectiveness and safety of studies from registration trials (RWE) compared with data obtained in real world studies conducted in Poland(Amaral et al., 2025; Placzke et al., 2023). An analysis of the Lower Silesian Melanoma Pilot program with quality indicators and patients' satisfaction level for the organization of oncological care in Poland for patients with cutaneous melanoma. The study has limitations that are partly reflected in the example of presented Polish RWE data – retrospective character of studies and selection bias. Cross-referencing of presented Polish data with currently valid 2024 ESMO, 2024 NCCN and 2022 PTOK guidelines assures high quality and reliability of presented knowledge on cutaneous melanoma. An expository paper with a narrative literature review(Amaral et al., 2025; Rutkowski et al., n.d.-b; Swetter et al., 2024).

2.3. AI.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Research results

3.1. Surgical Treatment

Although the primary method of treatment for localized cutaneous melanoma is surgery, the way in which surgery is applied to regional lymph nodes has changed dramatically from an almost universally aggressive to a less aggressive approach(Placzke et al., 2023; Ziętek et al., 2023). Initially, patients with melanoma underwent lymph node dissections based on the predicted surgical margins required to potentially cure the patient. Following biopsy of the primary lesion, wide local excision of the melanoma would follow. This involves the surgical removal of the original melanoma and a rim of apparently normal skin and subcutaneous tissue(Amaral et al., 2025; Caraviello et al., 2025b; Rutkowski et al., n.d.-b; Swetter et al., 2024). Contemporary international guidelines (ESMO, NCCN, ASCO) and Polish expert recommendations (PTOK) mandate that the dimensions of the excision margins be strictly tailored to the Breslow thickness of the primary tumor as determined by the initial excisional biopsy. For patients with melanoma in situ, an excision margin of 0.5 cm is suggested. Individuals with lesions that are 2.0 mm or less in thickness should have a 1.0 cm excision margin performed. For lesions greater than 2.0 mm in thickness, a 2.0 cm clinical excision margin is indicated. While in the past the commonly accepted excision margin for local treatment of cutaneous melanoma was 3 to 5 cm in width, multiple, prospective, randomized studies have established that smaller margins are adequate to provide local control while decreasing the surgical morbidity, preserving function, and improving aesthetics for patients requiring surgical therapy for localized melanoma(Amaral et al., 2025; Márquez-Rodas et al., 2024; Swetter et al., 2024).

A revolution has occurred in the surgical management of regional lymph nodes in patients with melanoma. Pathological staging of lymph nodes has evolved to include sentinel lymph node biopsy (SLNB) for clinically node-negative patients with intermediate thickness melanoma ($\geq$ 0.8 mm) and ulcerated thin lesions ($<$ 0.8 mm). The pathological examination of the sentinel lymph node (SLN) is the most important prognostic factor for patients with melanoma(Aldenhoven et al., 2022; Caraviello et al., 2025b; Placzke et al., 2023; Ziętek et al., 2023). Patients with lymph node-positive disease have the worst prognosis with highest risk of local/regional recurrence. In the past, a positive SLNB mandated immediate completion lymph node dissection (CLND) to evaluate the full extent of nodal involvement. However, results from the landmark MSLT-II and phase III DeCOG-SLT randomized trials have demonstrated that while CLND may improve regional control (Recurrence-Free Survival in the nodal basin), it offers no benefit in terms of Melanoma-Specific Survival (MSS) or Overall Survival (OS) compared to active surveillance(Caraviello et al., 2025b; Frich et al., 2021; Placzke et al., 2023; Ziętek et al., 2023).

Consequently, both international (ESMO, NCCN) and Polish (PTOK) guidelines no longer routinely recommend CLND following a positive SLNB. The preferred standard of care is now active surveillance, which consists of regular regional nodal basin assessment via ultrasound every 4 months for the first 2 years and every 6 months for the subsequent 3 years. Radical therapeutic lymphadenectomy is primarily reserved for patients with macroscopic, clinically or radiologically detected nodal disease, or for specific high-risk cases determined by a multidisciplinary team(Amaral et al., 2025; Márquez-Rodas et al., 2024; Rutkowski et al., n.d.-b).

3.2.Adjuvant Therapy

There have been significant updates in adjuvant systemic therapy for high-risk patients with melanoma over the last year. Adjuvant therapy is now indicated for patients with resected Stage III and Stage IV melanoma as well as those with high-risk Stage IIB and IIC (T3b–T4b N0 M0) (Amaral et al., 2025; Caraviello et al., 2025b; Seth et al., 2023a). Anti-PD-1 therapy, specifically 12 months of nivolumab (Opdivo) or pembrolizumab (Keytruda), has become the new standard of care for these patients post-surgery. Two phase III trials have been completed to evaluate the use of pembrolizumab and nivolumab in high-risk Stage IIB/C patients to prevent local or in-transit recurrence or distant metastasis (Patel et al., 2023). The results of these trials have been presented. Specifically, the CheckMate 76K trial showed that nivolumab improved 12-month RFS to 89% vs 79% with placebo ((Kirkwood et al., 2023; Márquez-Rodas et al., 2024; Seth et al., 2023).

Anti-PD-1 (nivolumab or pembrolizumab) induces durable RFS and DMFS in patients with Stage III and resected Stage IV melanoma, and such efficacy is independent of BRAF mutation status (Amaral et al., 2025; Ziętek et al., 2023a). For patients with BRAFV600 mutation, a highly effective alternative to anti-PD-1 remains dabrafenib plus trametinib for 1 year based on the 5-year RFS data of the COMBI-AD trial (52% vs 36% placebo) (Amaral et al., 2025; Rutkowski et al., n.d.). Patients and their healthcare providers must be aware of the distinct toxicity profiles associated with both treatment options. Targeted therapy may result in a steeper initial reduction in recurrence risk within the first year of treatment, whereas immunotherapy has a

slower growth of DMFS and RFS reduction, followed by a plateau, and some patients may have durable long-term protection. The CheckMate 915 trial demonstrated that the combination of nivolumab and ipilimumab did not improve RFS in patients with Stage IIIB-D/IV melanoma but was associated with a significantly higher rate of grade 3/4 TRAEs ((Nathan et al., 2021; Wolchok et al., 2021)Amaral et al., 2025; Weber et al., 2022).

3.3. Systemic Treatment of Advanced Melanoma

Management of unresectable or metastatic (Stage IV) melanoma has dramatically improved in the last decade. Combination systemic therapy can result in long-term disease control and even a cure in a subset of patients (Long et al., 2024; Seth et al., 2023a; Wolchok et al., 2025). For patients with unresectable or metastatic melanoma, the combination of a PD-1 inhibitor (nivolumab) and a CTLA-4 inhibitor (ipilimumab) is considered first-line standard of care, providing superior survival compared with single-agent ipilimumab. The final 10-year follow-up from the landmark CheckMate 067 trial shows that for patients treated with the combination of nivolumab and ipilimumab, the median overall survival was 71.9 months, with 43% of patients alive at 10 years, and 31% of patients experienced prolonged progression-free survival. This median overall survival of 71.9 months more than doubles the 8-month survival that was reported just over a decade ago with single-agent ipilimumab (Amaral et al., 2025; Wolchok et al., 2025, 2021).

Over the last year, first-line management has continued to evolve to include more targeted and immunotherapeutic approaches. In addition to the continued use of combined BRAF/MEK inhibitors for BRAF V600-mutated disease, checkpoint inhibitor combinations have solidified their role as primary treatment options. Data from the RELATIVITY-047 clinical trial demonstrated that the combination of relatlimab (a LAG-3 inhibitor) plus nivolumab significantly increased median progression-free survival (PFS) to 10.1 months compared to 4.6 months with nivolumab monotherapy. Long-term updates from this trial show that the 4-year PFS rate was maintained at 30.6% for the combination versus 23.6% for nivolumab alone. This dual inhibition also presents a more manageable toxicity profile compared to the nivolumab-ipilimumab triplet, providing a valuable alternative for untreated patients (Amaral et al., 2025; Lipson et al., 2025; Tawbi et al., 2022).

The assessment of pathological complete response (pCR) has emerged as a powerful prognostic indicator for overall survival, particularly in the neoadjuvant setting, and is a focus for future clinical trial endpoints. Furthermore, the 7-year update of the COLUMBUS trial continues to demonstrate durable outcomes for the targeted combination of encorafenib plus binimetinib, with a median overall survival of 33.6 months and 27.4% of patients alive at 7 years ((Patel et al., 2023)Czarnecka et al., 2025; Schadendorf et al., 2024). While immunotherapy is often preferred upfront, sequential trials such as DREAMseq and SECOMBIT have shown that starting with combination immunotherapy (Nivo/Ipi) followed by targeted therapy upon progression is associated with improved survival due to the durable responses initiated by the immunotherapy. Preliminary evidence also suggests that dual checkpoint inhibition (Nivo/Relatlimab) may have potential activity in pretreated settings or rare subtypes, though definitive data for uveal melanoma (UML) are still required (Lipson et al., 2025; Meric-Bernstam et al., 2024; Nathan et al., 2021; Rogala et al., 2022; Tawbi et al., 2022).

3.4. Neoadjuvant Therapy

For patients with localized high-risk Stage III and Stage IV melanoma, the use of neoadjuvant (perioperative) therapy is being explored. The tumor immune microenvironment is enhanced by administering systemic therapy prior to surgery to treat a larger burden of tumor antigens. Findings from the phase II SWOG S1801 trial show that three doses of neoadjuvant pembrolizumab (PB- neo) in combination with postoperative PB and continued adjuvant therapy significantly improved event-free survival (EFS) over adjuvant PB given alone, with 2-year rates of 72% vs 49%(Amaral et al., 2025; Szlasa et al., 2024).

We report our experiences with combination immunotherapy trials, NADINA, PRADO and OpACIN-neo. Notably, patients who responded with pathological complete response (pCR) or major pathological response (MPR) to neoadjuvant combination immunotherapy (ipilimumab plus nivolumab) had excellent long-term survival outcomes. Future trials will aim to utilize combination immunotherapy in the neoadjuvant setting, potentially even obviate the need for radical surgery and adjuvant chemotherapy in the ‘major responders’ with <10% viable tumour within the index node. The use of neoadjuvant pembrolizumab or nivolumab plus ipilimumab in patients with clinically resectable Stage IIIB–IV melanoma is now supported by ASCO and NCCN guidelines(Amaral et al., 2025; Larkin et al., 2022).

Table 1. Major Systemic Treatment Options in Advanced and Adjuvant Settings

Therapy Type	Agents	Primary Indications
Anti-PD-1 Immunotherapy	Nivolumab, Pembrolizumab	Regardless of BRAF status; Adjuvant or First-line
Combined Immunotherapy	Nivolumab + Ipilimumab	Preferred for CNS metastases or aggressive disease
Targeted Therapy (BRAF/MEK)	Dabrafenib + Trametinib	Exclusively for BRAF V600 mutated patients
Novel Combination (LAG-3)	Nivolumab + Relatlimab	New first-line option (EMA approved for PD-L1 <1%)

Current therapeutic algorithms (ESMO, ASCO, NCCN, and PTOK) categorize systemic treatments based on mutational status and disease aggressiveness (Amaral et al., 2025; Rutkowski et al., n.d.-b; Swetter et al., 2024)

3.5. Comparison: Poland vs International Practice

Implementation of international standards in the field of cancer in Poland is on a "dual-speed". In reference centers for particular types of cancer recommendations for treatment of patients are strictly based on guidelines prepared by the Polish Society of Clinical Oncology (PTOK) in consultation with leading specialists from home and abroad. The largest center of this kind in Poland is the Maria Skłodowska-Curie National Research Institute of Oncology (NIO-PIB), with its headquarters in Warsaw and branches in other regions of the country. However, in terms of how far the disease has progressed when it is first registered in the population, compared to cancer worldwide there are still significant differences. In Lower Silesia, the stage of cancer detection is higher than the countrywide average, and it equals that observed in reference centers, as Dr. med. Janusz Niklinski, Director of the Lower Silesian Oncology, Pulmonology and Hematology Center (DCO Wrocław), informed (Placzke et al., 2023; Ziętek et al., 2022, 2023).

Access to treatment has fundamentally changed due to National Drug Program "B.59" as well as "Emergency Access to Drug Technologies" (RDTL). Until 2018, modern systemic therapies for patients with melanoma could only be offered in clinical trials. In 2018, National Drug Program "B.59" introduced coverage of anti-PD-1 (nivolumab, pembrolizumab) and BRAF/Mek target IDH inhibitors (dabrafenib/trametinib) for adjuvant and metastatic melanoma treatment. Moreover, access to treatment differs from that worldwide. For example, a combination of nivolumab with relatlimab (LAG-3 inhibitor) is approved and registered in the European Union, but is not reimbursed in Poland(Amaral et al., 2025; Czarnecka et al., 2025; Rutkowski et al., n.d.-b; Ziętek et al., 2023).

Based on real-world evidence (RWE) from nationwide Polish multicenter studies conducted by NIO-PIB and DCO Wrocław, there has been global surgical de-escalation in the management of patients with positive SLNB. The rate of CLND decreased from 88% in 2017 to 41% in 2021, while the rate of using adjuvant systemic therapy increased from 11% in 2017 to 51% in 2021. Adjuvant therapies were effective and well-tolerated in the routine practice of surgeons. Two-year OS and RFS rates amounted to 86.7% and 61.4%, respectively, comparable to results of international registration trials CheckMate 238 and KEYNOTE-054 (Placzke et al., 2023; Rogala et al., 2022).

All existing studies, reported in various Polish medical journals, point to the fact that despite appropriate therapy, the problem of early detection of melanoma is the most important factor determining the long-term survival of patients in Poland. Why this is the case is not clear, but it probably results from a combination of patient- and public-based as well as physician-based factors, i.e., the unawareness of skin warning signs of melanoma. This "Polish paradox" of late detection contrasts sharply with treatment outcomes reported from Western Europe. Mean and median Breslow thicknesses in some Polish series exceeded 3.2 mm and 2.0 mm, respectively, which is more than an overall average for Western Europe (usually <1.0 mm). The data presented here show that 43% of the study patients were at Stage T4 at the time of diagnosis(Amaral et al., 2025; Szostak et al., 2024; Ziętek et al., 2023).

Despite the systemic obstacles to the proper treatment of patients with melanoma, organizational innovations can be effective in overcoming them. Based on real-world evidence, the management of patients registered in the healthcare system has been significantly improved by introducing the Lower Silesian Melanoma Pilot program to the existing diagnostic and treatment infrastructure at the Lower Silesian Oncology,

Pulmonology and Hematology Center (DCO Wrocław). This center serves a regional population of approximately 2.9 million people. The program introduced medical coordinators to navigate the patient pathway and implemented synoptic histopathological analysis protocols to standardize diagnostic reporting. As a result, the timeliness of initial diagnostics within the mandated 3-week "DILO" fast-track period was maintained at 87.8%. On the other hand, real-world data from Polish cohorts indicate that severe (Grade ≥ 3) treatment-related adverse events (TRAEs) associated with systemic therapy have a significant negative impact on survival; specifically, the 2-year overall survival (OS) rate for patients experiencing these events decreased to 60.6%. Therefore, the continuous monitoring of TRAEs and expert supervision in routine clinical practice are strongly warranted to maximize therapeutic benefits(Placzke et al., 2023; Ziętek et al., 2022, 2023, 2025).

3.6. Future Perspectives

Cutaneous melanoma management is at a crossroads. Moving on from standardisation towards individualised patient management using molecular biomarkers, novel immunotherapies and emerging digital technologies is our objective in the face of ongoing therapeutic resistance.

3.6.1. Personalized Medicine and Emerging Biomarkers

While BRAF mutation testing is mandatory for the management of patients with advanced disease future strategies will require a more multi-modal approach to define a patient's unique biological risk. Within this framework, the role of circulating tumor DNA (ctDNA) as a surrogate marker for disease burden and molecular residual disease (MRD) is becoming increasingly prominent. Sensitive assays for the measurement of ctDNA have demonstrated the ability to detect relapse before clinical or imaging evidence is identified, and preoperative levels of ctDNA are now recognized as a strong prognostic factor in patients with high-risk Stage III cutaneous melanoma(Caraviello et al., 2025b; Cybulska-Stopa et al., 2022; Schadendorf et al., 2024). Another pivotal biomarker is tumor mutational burden (TMB), defined as the total number of somatic mutations per megabase of exome sequence. TMB is significantly elevated in cutaneous melanoma, primarily due to cumulative ultraviolet-induced mutations, and correlates with higher rates of objective response and improved progression-free survival (PFS) for patients treated with immune checkpoint inhibitors (ICIs). Parallel to genomic markers, the biological drivers of tumor progression and their interactions within the tumor microenvironment (TME) have drawn increased attention (Matkowski et al., 2025; Sorino et al., 2024). Specifically, the increased expression of certain matrix metalloproteinases (MMPs) including MMP-1, -2, -9, and -13 has been shown to enhance the invasive and metastatic potential of the tumor by digesting the extracellular matrix (ECM)(Lazar et al., 2024). These enzymes represent potential individualized therapeutic targets for future synthetic inhibitors. Furthermore, host factors such as sarcopenia (loss of skeletal muscle mass), which is prevalent in approximately 40.23% of melanoma patients, have been identified as strong negative prognostic factors for overall and relapse-free survival in patients receiving immunotherapy(Jarell et al., 2026; Surov et al., 2022). The synthesis of these molecular, environmental, and host-related data points will be essential for the next generation of precision oncology in melanoma care.

3.6.2. mRNA Neoantigen Vaccines

Individualized vaccines have recently emerged as promising adjuvants in cancer treatment. First introduced as checkpoint inhibitors, targeted immune therapy has evolved into active, individualized vaccination. One example thereof is the individualized neoantigen therapy mRNA-4157 (V940), which encodes for up to 34 patient-specific, tumor-derived neoantigens. In the phase II KEYNOTE-942 trial, the combination of mRNA-4157 and pembrolizumus significantly improved pFS in 146 patients with high-risk resected Stage IIB to IV melanoma(Sorino et al., 2024). Promising pFS results are currently being validated in the global, phase III INTerpath-001 trial(Amaral et al., 2025; Caraviello et al., 2025b; Meric-Bernstam et al., 2024; Tawbi et al., 2022).

3.6.3. Combination Therapies and Overcoming Resistance

Only 50%–80% of patients with advanced melanoma achieve a complete or partial response to anti-PD-1 therapy, leaving 30%–50% of the patients with primary resistance to this effective treatment approach(Wong et al., 2025). Continued exploration of new combinations is thus warranted. With the recent approval of the LAG-3 inhibitor relatlimab plus nivolumab as a new first-line standard of care for patients with advanced melanoma, the RELATIVITY-047 trial expands our knowledge on dual checkpoint inhibitors(Lipson et al., 2025; Márquez-Rodas et al., 2024; Tawbi et al., 2022). Relatlimab plus nivolumab nearly doubled median progression-free survival versus nivolumab plus IgG4 mAb control and provided a toxicity profile that was intermediate to that of the combination with ipilimumab.

There is growing interest in the potential benefits of tumour-infiltrating lymphocyte (TIL) therapy, exemplified by lifileucel (PDT-001). TILs may represent a potentially highly effective treatment for patients with metastatic melanoma who have failed ICIs and/or other targeted therapies. Furthermore, lifileucel, the first cellular therapy to receive FDA approval for treatment of metastatic melanoma, has generated durable systemic responses in patients with refractory disease. The use of oncolytic viruses (OVs) are also gaining attention for the treatment of patients with melanoma. While local administration of the approved T-VEC has shown promise, next-generation OVs such as RP1 (vusolimogene odomaparepvec) are already demonstrating deep and durable systemic activity in patients with metastatic melanoma who have failed prior PD-1 therapy(Amaral et al., 2025; Caraviello et al., 2025b; Wong et al., 2025).

3.6.4. Role of Artificial Intelligence in Decision-Making

Artificial Intelligence (AI) and deep learning are becoming more prominent tools in image analysis to assist in the diagnostic and prognostic pathway, potentially decreasing variability associated with visual inspection. Image classification for the purpose of melanoma detection has been achieved with high accuracy. Convolutional Neural Networks (CNNs) such as ResNet-101 and DenseNet-II have achieved diagnostic accuracy greater than 95% for the binary classification of melanoma versus non-melanoma. Interestingly, some studies have reported AI/machine learning to be more accurate than board-certified dermatologists(Al Zegair et al., n.d.-b; Naseri & Safaei, 2025b).

The future clinical integration of AI includes:

1. Dermoscopic and Histopathological Analysis: It helps to identify the ugly duckling lesion and determines Breslow thickness and mitotic index.
2. Clinical Decision Support Systems (CDSS): Next generation software that will utilise the power of Artificial Intelligence (AI) to combine clinical, genetic and longitudinal data to predict long-term patient outcomes such as recurrence risk and survival to plan follow-up.
3. Primary Care Triage: mHealth primary diagnostic Crowd sourcing smartphone apps that support the detection of skin cancer in the general population can result in an enhanced rate of detection. However, such tools are likely to result in a large number of benign lesions being referred for specialist diagnosis and would require clinical integration.

The future of melanoma is to bring all these advances together in one coordinated multidisciplinary approach. This includes ongoing genomic monitoring and personalised immunotherapy, including mRNA vaccines and TILs. It will require daily AI diagnostics(Al Zegair et al., n.d.-b; Caraviello et al., 2025b).

Table 2. Melanoma Clinical Guidelines and Machine Learning Models for Diagnosis

Disease Stage	Diagnostic/Predictive Approach	Recommended Treatment or Model Architecture	Dataset or Clinical Population	Performance Metric or Outcome	Source
Stage IV (metastatic)	First-line systemic therapy	Nivolumab plus Ipilimumab followed by Nivolumab	Patients with unresectable or metastatic cutaneous melanoma	More than 70% 1-year survival rate	(Amaral et al., 2025; Caraviello et al., 2025b; Seth et al., 2023)
Stage IV (metastatic)	First-line systemic therapy (targeted)	BRAF plus MEK inhibitors (Dabrafenib + Trametinib)	Patients with BRAF V600-mutant unresectable or metastatic melanoma	High objective response rate (approx. 70%)	(Caraviello et al., 2025b; Rutkowski et al., n.d.-b; Seth et al., 2023)
Stage III or IV (progressive/ advanced)	First-line systemic therapy	PD-1 blockade CTLA-4 blockade, LAG-3 blockade or BRAFi-MEKi	Patients with unresectable stage III or IV cutaneous melanoma	Median OS 71.9 months for Nivolumab-Ipilimumab in CheckMate 067 trial	(Al Zegair et al., n.d.-b; Weber et al., 2022)

Disease Stage	Diagnostic/Predictive Approach	Recommended Treatment or Model Architecture	Dataset or Clinical Population	Performance Metric or Outcome	Source
Stage IIIB-IV (resectable)	Neoadjuvant therapy	Pembrolizumab followed by resection and adjuvant Pembrolizumab	313 patients with resectable stage IIIB to IV melanoma	2-year EFS rate of 72% in neoadjuvant arm vs 49% in adjuvant-only arm; EFS significantly longer	(Amaral et al., 2025; Seth et al., 2023; Swetter et al., 2024)
Stage III (resectable)	Neoadjuvant therapy	Neoadjuvant Nivolumab-Ipilimumab vs Adjuvant Nivolumab	423 patients with biopsy-proven, resectable stage III melanoma	Estimated 18-month EFS: 80.8% in neoadjuvant vs 53.9% in adjuvant group	(Amaral et al., 2025)
Stage III (resectable)	Neoadjuvant therapy	Nivolumab + Ipilimumab (Flip-dose)	OpACIN-neo trial	77% Pathologic Response Rate; 3-year RFS: 82%	(Amaral et al., 2025)
Stage III (resectable)	Neoadjuvant therapy	Nivolumab + Relatlimab	30 patients (Phase II study)	57% pCR rate; 70% pRR; 2-year RFS: 92%	(Amaral et al., 2025)
Stage III (resectable)	Neoadjuvant therapy	Dabrafenib + Trametinib	21 patients (MD Anderson Phase II study)	Median EFS: 19.7 months vs 2.9 months (Adjuvant group);	(Amaral et al., 2025)
Stage IIIB-IVM1a	Intralesional therapy	Talimogene laherparepvec (T-VEC)	150 patients with unresectable, cutaneous, subcutaneous, and nodal lesions (OPTiM and Phase II trials)	Significant improvement in durable response rate, OS, and 2-year RFS (29.5% vs 16.5% surgery alone)	(Amaral et al., 2025)
Stage III (resected)	Adjuvant systemic therapy	PD-1 inhibitors or BRAF/MEK inhibitors	Stage III patients	5-year survival rates of 77% and 69% for 10-year	(Amaral et al., 2025; Caraviello et al., 2025b; Seth et al., 2023)
Stage III (SLNB-positive)	Clinical Study / Real-world analysis	Dabrafenib + Trametinib (BRAF inhibitors)	557 melanoma patients from 7 Polish comprehensive cancer centers (2017-2021)	RFS (HR: 0.20, p=0.002)	(Ziętek et al., 2023)
Stage III (SLNB-positive)	Clinical Study / Real-world analysis	Anti-PD-1 (Nivolumab or Pembrolizumab)	557 melanoma patients from 7 Polish comprehensive cancer centers (2017-2021)	RFS (HR: 0.50, p=0.015)	(Ziętek et al., 2023)
Stage IIB or IIC (resected)	Adjuvant systemic therapy	Pembrolizumab or Nivolumab	Patients with completely resected AJCC8 pathological stage IIB-IIC melanoma	Reduced risk of recurrence (HR: 0.53-0.64); 36-month RFS 76.2% vs 63.4% (placebo)	(Amaral et al., 2025; Márquez-Rodas et al., 2024; Seth et al., 2023)

Disease Stage	Diagnostic/Predictive Approach	Recommended Treatment or Model Architecture	Dataset or Clinical Population	Performance Metric or Outcome	Source
Stage I-IV	Surgical Staging	Sentinel Lymph Node Biopsy (SLNB)	Patients with Breslow thickness > 1 mm or high-risk features	Correct staging and prognostic prediction for 5- and 10-year survival	(Caraviello et al., 2025b)
Stage IIC - III	Clinical Trial (BRIM8)	Vemurafenib	Patients with stage IIC and stage III BRAF mutation-positive melanoma	Did not meet primary endpoint of Disease-Free Survival (DFS)	(Amaral et al., 2025)
Early detection (Stage I-III)	Classification by tumour thickness	Modified CNN using SMTP	Dataset of 250 melanoma cancer images categorized by size	Accuracy: 0.96; Sensitivity: 0.9804;	(Al Zegair et al., n.d.-b; Naseri & Safaei, 2025a)

Table 2. provides a comprehensive synthesis of traditional dermatological standards and the emerging role of artificial intelligence (AI) in oncology. It contrasts established clinical diagnostic rules, such as the ABCDE criteria (Asymmetry, Border, Color, Diameter, Evolution) and the "ugly duckling" sign, with the results of advanced machine learning (ML) and deep learning (DL) studies. The analysis incorporates diagnostic and staging recommendations from major oncological organizations, including ESMO, NCCN, ASCO, and PTOK, emphasizing standard requirements for dermoscopy and histopathological analysis.

4. Discussion

Management of cutaneous melanoma has undergone a paradigm shift from a primarily surgical-based disease management strategy to an early and very potent systemic-based disease management strategy, underscored by recent major clinical trials and real-world evidence. A safe de-escalation of surgical efforts in the regional nodal basin, most notably the omission of completion lymph node dissection (CLND) following an initial positive sentinel lymph node biopsy (SLNB), is possible only because of the unprecedented levels of efficacy delivered by adjuvant immune checkpoint inhibitors and targeted therapies (Matkowski et al., 2025; Placzke et al., 2023; Ziętek et al., 2023a).

What is the international view on the clinical role of CLNB for SLNB-positive patients? The 2024 ESMO Clinical Practice Guideline for Melanoma recommends that CLNB is “no longer a standard of treatment” for SLNB-positive patients provided that active ultrasound surveillance of the lymphatic basin is rigorous (Amaral et al., 2025). The 2024/2025 NCCN Clinical Practice Guidelines in Oncology for Melanoma states that the performance of CLND is “not recommended” in patients with SLNB-positive for melanoma provided a “rigorous surveillance” of the basin is performed (Frich et al., 2021; Swetter et al., 2024a). The 2022 Polish Society of Clinical Oncology (PTOK) Surgical Management of Melanoma Guidelines are also in line with the international standards regarding CLNB (Rutkowski et al., n.d.). Nevertheless, there is an “implementation gap” in the Polish health system. Even though all surveyed Polish centers rapidly introduced surgical de-escalation protocols, the rates of CLND fell from 88% in 2017 to 41% in 2021, which is lower than the rates recommended by international guidelines. This phenomenon can only be described as the “Polish paradox” of late-stage melanoma diagnosis.

Survival of patients with melanoma in Poland may be poorer than in some Western European countries, mainly because of late diagnosis and not of lack of access to proper and timely treatment. In a nationwide study all 1011 melanoma patients diagnosed in Poland in the period 2000-2006 were evaluated. Mean Breslow thickness was 2.0 mm. More than 43% of patients had Stage T4. Delay in primary screening and patient ignorance of skin self-examination are likely responsible for late diagnosis. However, within a pilot integrated 'DILO' fast-track treatment programme, a medical coordinator has made it possible to diagnose and start the treatment within three weeks in 87.8% of cases. Urgent measures for primary prevention are thus needed. Public health campaigns should inform patients about risk factors for melanoma and how to perform skin self-examination (Márquez-Rodas et al., 2024; Naseri and Safaei, 2025a).

Current systemic therapies for melanoma have evolved to achieve durable long-term survival, but at the cost of significant toxic side effects. Building on the 10-year update to the CheckMate 067 trial, dual-checkpoint blockade with nivolumab and ipilimumab continued to deliver durable medium long-term overall

survival, with median follow-up of 71,9 months, though high rates of grade 3/4 treatment-related adverse events (TRAEs) remained a significant concern. The search to further optimize efficacy with manageable toxicity in patients with previously untreated melanoma has remained an important area of investigation. In the RELATIVITY-047 trial, the LAG-3 inhibitor relatlimab in combination with nivolumab (relatlimab + nivolumab) significantly improved progression-free survival (10,1 months) compared with nivolumab (4,6 months) alone (Lipson et al., 2025; Márquez-Rodas et al., 2024; Tawbi et al., 2022).

Another relevant group of patients for RWE data from Polish centers are those for whom patient selection and tolerance to therapy in the "real world" practice setting is most relevant. Although in the Polish adjuvant RWE study any TRAE (>10%) was associated with improved RFS, severe (Grade ≥ 3) TRAEs were associated with a marked decrease in OS (60.6% below expectation at 2 years). This finding supports the need for expert multidisciplinary evaluation and thoughtful patient selection, particularly based on PS and comorbidities.

Host factors and the tumour microenvironment (TME) contribute to therapy resistance. Sarcopenia is a reduction of skeletal muscle mass and recent meta-analyses have demonstrated that patients with sarcopenia have poorer overall survival (OS) and progression-free survival (PFS) on immunotherapy (Amaral et al., 2025; Al Zegair et al., n.d.). In this review we discuss how melanoma cells interact with the stromal compartment of the skin to create a tumour microenvironment that supports invasive growth and resistance to drugs through modulation of cancer-associated fibroblasts (CAFs) and increased production of MMPs (Amaral et al., 2025).

Novations in the digital and molecular area can be applicable to the current problems in dermatology in Poland. Potential benefits of introducing artificial intelligence to support clinical diagnostic process include detection of melanoma at an early stage for the patients, to relieve pressure on specialists from a large flow of consultations in primary care. Some of deep learning architectures have been tested and achieve high accuracy in classification of melanoma. In addition, circulating tumour DNA (ctDNA) and detection of molecular residual disease (MRD) are rapidly evolving tools for monitoring of patients and early detection of relapse. An example of this is COMBI-AD biomarker study, which demonstrated that presence of ctDNA during treatment for localized melanoma is associated with relapse.

While the studies utilizing real-world evidence (RWE) to address important questions in skin cancer have many positive attributes, there are several areas that need attention (Amaral et al., 2025; Cybulska-Stopa et al., 2022; Al Zegair et al., n.d.). To begin, the studies to date have been performed retrospectively. There is a paucity of data regarding patients with BRAF mutations who have lost response to first-line immunotherapy. Going forward, the hope would be to perform these studies as "proof of concept" to allow for rapid progression to prospective studies that will ultimately benefit all patients with skin cancer. This will require embracing of a model of personalized medicine utilizing a combination of tumor and host biomarkers of fitness, as well as artificial intelligence–driven decision support to help optimize treatment to maximize the chance of a long-term cure for every patient with skin cancer (Amaral et al., 2025; Al Zegair et al., n.d.).

5. Conclusions

The treatment of skin melanoma has changed a lot in recent years. Now, doctors use a team approach that focuses on treating the whole body early on and avoiding radical surgery whenever possible. This change is clear in how doctors used to always remove more lymph nodes after finding cancer in the first node they checked, but now they often just watch those nodes closely with ultrasound instead. Studies have shown that this approach works just as well for keeping patients alive, but it causes a lot less harm from surgery in the long run. Also, new medicines that are very effective have been added to treatment plans for patients with melanoma that has spread or is at high risk of coming back. These medicines have changed the outlook for patients with advanced melanoma, making it a condition that can be managed over time for many people.

Improving cancer care is crucial, and following established guidelines is key. Organizations like the European Society for Medical Oncology, the National Comprehensive Cancer Network, and the Polish Society of Clinical Oncology provide these guidelines. In Poland, top cancer centers like the Maria Skłodowska-Curie National Research Institute of Oncology and the Lower Silesian Oncology, Pulmonology and Hematology Center are working to meet international standards. This means patients get high-quality care that's on par with global benchmarks. However, there's still a big problem in Poland - many people are diagnosed with cancer at a late stage, which affects how many people die from the disease. Finding cancer early is critical for saving lives. If doctors can detect cancer sooner, patients have a much better chance of being cured - up to 95% in some cases. So, it's essential to combine excellent medical care with public health efforts to raise awareness about early detection. One way to do this is by teaching people about the "ugly duckling" sign, which can help

them identify potential skin cancers early. By working together, we can improve cancer outcomes in Poland and save more lives.

As we look to the future, it's clear that artificial intelligence and personalized medicine will play a big role in shaping the next phase of melanoma care. New algorithms, like DenseNet and ResNet, are really good at diagnosing melanoma - they can get it right more than 95% of the time. This means they could help standardize how we look at skin samples and tissue, and even help doctors in primary care settings decide who needs more testing. At the same time, we're moving towards treating each patient as an individual, using special markers like circulating tumor DNA and tumor mutational burden to guide our decisions. We're also getting closer to using personalized vaccines and new combinations of therapies to attack the cancer. The goal is to combine the best of both worlds - following standardized guidelines and using high-precision personalized medicine - to reduce the number of people affected by this aggressive cancer and help all patients live longer, healthier lives. By bringing together these different approaches, we can make a real difference in the fight against melanoma.

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Conceptualization, W.Ł and J.K; methodology, M. J and J.C; formal analysis, L. K and J.N; investigation, W.Ł and M.M; writing original draft preparation, W. Ł and K.J; writing review and editing, J.C; supervision, W.Ł. All authors have read and agreed to the published version of the manuscript.

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All AI technologies were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of analytical findings, and conclusions were determined exclusively by human experts in clinical medicine and formal logic. The AI tools supported efficiency in data processing, pattern recognition, and language refinement and did not replace human scientific judgment or responsibility for the content of the manuscript.

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