Expert recommendations on diagnostic--therapeutic management of melanoma patients

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According to the authors and editors, this report contains the best justified principles of diagnostic and therapeutic procedures prepared on the basis of the scientific value of evidence and recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, current possibilities for reimbursement of individual procedures should be determined.

The quality of scientific evidence

I — Evidence from at least one large randomized controlled clinical trial (RCT) of high methodological quality (low risk of bias) or meta-analysis of properly designed RCTs without significant heterogeneity

II — Small RCTs or large RCTs with risk of bias (lower methodological quality) or a meta-analysis of such studies or RCTs with significant heterogeneity

III — Prospective cohort studies

IV — Retrospective cohort studies or case-control studies

V — Uncontrolled studies, case reports, expert opinions

2. Strength of recommendations

1 — Recommendation based on high-quality evidence on which unanimity has been achieved or a high level of expert team consensus

2A — Recommendation based on lower-quality evidence on which unanimity has been reached or a high level of expert team consensus

2B — Recommendation based on lower-quality evidence on which moderate expert consensus has been achived

Methodology

Review of all phase II and III clinical trials available in PubMed and published between 1990 and 2021 and containing the term "melanoma" and current recommendations of the European Society Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and the Polish Society of Clinical Oncology (PTOK).

Part I.
Skin and mucosal melanoma

Summary

Diagnostics

— Dermatoscopic examination (dermoscopy) is recommended for the assessment of skin lesions, especially before their planned excision.
— In the case of skin lesions, an excisional biopsy should be performed (in most cases under local anesthesia), with a minimal surgical margin of 1–2 mm (III, 2A).
— The elements of microscopic histopathological reporting of primary cutaneous lesions should obligatorily include (1) infiltration thickness in mm according to Breslow in mm, (2) presence or absence of ulceration, (3) number of division figures per 1 mm^2 (mitotic index), (4) pT staging, (5) growth phase, (6) presence or absence of microscopic satellite foci, (7) peripheral and deep surgical margin (assessment of radicality of surgical procedure).
— Molecular testing for the presence of *BRAF* gene mutations is mandatory in patients with stage III (operable and non-operable) and IV (I, 1) and recommended for stage IIC.

Staging

— Physical examination with a careful assessment of the entire skin (especially the assessment of other suspected pigmented lesions, satellite or in-transit nodules, regional lymph nodes, and possible distant metastases).
— In higher stages, it is recommended to perform an ultrasound examination (US) and computed tomography (CT), and/or positron emission tomography (PET) for proper staging.

Treatment for stage I–III melanoma (resectable)

— Radical excision of the scar after excisional biopsy of the primary lesion is recommended in all patients with appropriate resection margins (melanoma in situ 5 mm, melanoma with Breslow thickness ≤ 2 mm — 1 cm, melanoma with Breslow thickness > 2 mm–2 cm) (I, 1).
— Sentinel lymph node biopsy (SLNB) is recommended in the case of infiltration with Breslow thickness ≥ 0.8 mm or (micro) ulceration on melanoma surface, regardless of Breslow thickness (pT1b–T4b) (I, 1).
— Sentinel lymph node biopsy should be performed simultaneously with radical excision of the scar after melanoma excisional biopsy.
— Lymphadenectomy in the case of positive sentinel lymph node biopsy is not routinely recommended (I, 2A).
— Lymphadenectomy is indicated in the presence of metastatic melanoma in clinically detected lymph nodes (II, 2A).
— Systemic adjuvant therapy with immunotherapy (anti-PD-1: nivolumab or pembrolizumab) or targeted therapy (dabrafenib/trametinib, in the presence of *BRAF* gene mutation) is indicated in all patients with stage III after metastases resection or after resection of stage IV lesions (nivolumab) (I, 1).
— Radiotherapy as adjuvant treatment is not recommended (II, 1).

Treatment of stage III (inoperable) and stage IV

— For patients with metastatic disease, enrollment in clinical trials is the most appropriate treatment.
— Systemic treatment of patients with *BRAF V600* mutation includes BRAF inhibitor (in combination with MEK inhibitor) and, regardless of *BRAF* mutation status, immunotherapy anti-PD-1 (nivolumab or pembrolizumab), anti-CTLA-4 (ipilimumab) antibodies in monotherapy or in combination (nivolumab with ipilimumab) (I, 1).
— The optimal treatment sequence (especially in the presence of *BRAF* mutation) has not been definitely established yet.
— The use of combination therapy with BRAF and MEK inhibitors is associated with a high response rate (approximately 70%) and quick symptom resolution, while treatment with anti-PD-1 antibodies results in a lower response rate; however, responses are mostly long-term and persist even after discontinuation of therapy.

Follow-up after treatment

— Patient education regarding skin and lymph node self-examination.
— Medical history and physical examination, including a comprehensive skin assessment, especially the area of scar after resected melanoma and regional lymph nodes (every 3–6 months for the first 2–3 years, then every 3–12 months up to 5 years, and once a year after 5 years) (II, 2A).
— Ultrasound examination of regional lymph nodes every 4–6 months if a positive sentinel lymph node is detected without lymphadenectomy and if sentinel lymph node biopsy was not performed in the case of skin melanomas ≥ pT1b (every 4 months for the first 2 years, then every 6 months for the next 3 years, up to 5 years inclusive).
— In asymptomatic patients after 5 years of follow-up, imaging examinations are not recommended.
— The frequency and type of examinations, as well as the duration of the observation, should depend on individual risk of disease recurrence (II, 2A).

Epidemiology and etiology

Melanomas are malignant neoplasms originating from neuroectodermal melanocytic cells. In Poland, melanomas are relatively rare — the standardized incidence rate is about 6 per 100 000, which corresponds to about 3 800 cases per year in recent years (about 1800 in men and about 2000 in women). However, melanomas are neoplasms with the largest incidence growth rate, i.e. increase of newly diagnosed cases. In Poland, in the years 1980–2010, the number of cases increased almost threefold. The median age of onset is similar for both sexes and is approximately 50 years. Standardized mortality rates are around 2.1 per 100 000 in men and 1.4 per 100 000 in women, accounting for an estimated 700 and 710 deaths from melanoma among men and women, respectively, in recent years [1–3].

The following are considered to be the most important factors of the increased melanoma risk: (1) high exposure to ultraviolet (UV) radiation, both natural (sun rays, especially sunburn in childhood and young age) and artificial (e.g. tanning beds, solariums), (2) constant mechanical or chemical irritation, (3) low skin pigment and (4) genetic predisposition, e.g. familial atypical mole syndrome (FAMS) (III, 2A). Protection against excessive UV radiation represents the most important element of melanoma primary prevention (III, 2A).

In over 90% of cases, melanomas develop in the skin. However, melanocytes are also found in locations other than skin (epithelium of respiratory tract, digestive tract, and genitourinary mucous membranes, as well as uvea and meninges), which may lead to primary melanoma development also in these locations.

Mucosal melanomas are very rare neoplasms and account for up to 1% of all melanomas (several dozen cases are recorded annually in Poland). They mainly develop as tumors of head and neck (nasopharynx), gastrointestinal tract (most often in the anal area), and the genital area (mainly vulva and vagina) [4]. Melanomas of the mucous membrane are a condition which most commonly affects older patients (mean age of onset is about 70 years), although primary oral mucosal melanoma often occurs at an earlier age [5, 6]. Mucosal melanoma is more common in women than in men, mainly due to the development of the disease in the genital area. It is estimated that 20% of mucosal melanomas are multifocal [7], compared with less than 5% of skin melanomas [8]. About 40% of mucosal melanomas are colorless (amelanotic) while in the skin they occur in less than 10% of cases. Mucosal melanomas are characterized by an aggressive clinical course and poor prognosis. Most patients eventually develop distant metastases despite radical surgery. The 5-year survival rate in mucosal melanoma is only 25% [9].

In about 3% of cases [10] melanoma cells are found in the lymph nodes or other organs — the primary melanoma lesion cannot be determined and this is the so-called melanoma with an unknown primary (MUP) (T0). MUPs should be treated as cutaneous melanomas. At diagnosis, in approximately 80% of patients, skin melanoma is a local lesion, while the regional and metastatic stage is diagnosed primarily in approximately 15% and 5% of patients, respectively. The 5-year survival rates in early melanoma are 70–95%, and 30–70%, 20–40%, in regional and metastatic stage, respectively, despite using modern systemic treatment.

Advances in adjuvant and palliative treatment are still unsatisfactory in patients with metastatic cutaneous melanoma, and, therefore, melanoma should be detected at the earliest possible stage of the disease. Due to the localization, early identification of the primary lesion (microstaging I — excisional biopsy of the primary lesion) and regional lymph nodes metastases (microstaging II — sentinel lymph node biopsy) enable cutaneous melanoma radical treatment.

The primary and obligatory rule should be multidisciplinary team (MDT) management of melanoma patients. Team members should be experienced in the diagnosis and treatment of melanomas. Above all this roule should be applied to patients with stage III and IV melanomas [11, 12].

Diagnostics

Skin melanoma may be suspected when skin lesions develop *de novo* or on the basis of a pigmented nevus. The medical history should include questions about the condition of the skin, i.e. any changes in the existing skin moles, the appearance of new pigment spots and accompanying symptoms (e.g. pruritus), and factors increasing the risk of skin melanoma (e.g. sunburn, use of self-tanning beds — solarium, family history of melanomas and previous immunosuppressive treatment, or human immunodeficiency virus [HIV] infection). It should be emphasized that in more than 60% of melanomas diagnosed during clinical assessment, medical history is unrevealing.

Clinical symptoms are sometimes grouped into systems to facilitate diagnosis (Tab. 1). The best known is the American clinical system ABCDE, currently used mainly for educational purposes, as it allows identifying only part of melanomas, mainly superficially spreading melanomas, and significant part of advanced melanomas. It cannot be used as a screening diagnostic tool in

Table 1. ABCDE Rule allowing for the initial identification of some melanomas based on clinical examination without the use of additional diagnostic methods

ABCDE System
A (asymmetry) — melanoma is asymmetrical according to each axis of the lesion, unlike benign moles, which are usually round or oval, additionally presenting irregular shape with protrusions called islands
B (borders) — uneven and notched
C (color) — variety of colors (from different shades of brown to black, steely) with uneven pigment distribution, frequently with spot deposits (especially visible in dermatoscopy)
D (diameter) — higher than 5 mm or dynamics of morphological changes in the tumor
E (elevation or evolution) — elevation of surface above the level of surrounding epidermis. Thin melanomas (thickness ≤ 1 mm according to the Breslow scale) make it impossible to palpate protuberance compared to normal skin surrounding the lesion; more important than elevation of primary lesion is extension or evolution

clinical practice. The ABCDE clinical system does not allow for proper classification of about 50% of melanomas (especially early melanomas < 5 mm in diameter, nodular melanomas, usually without color heterogeneity or border irregularity, as well as nonpigmented [amelanotic] melanomas and scalp lesions) [1].

However, the most important element allowing early diagnosis of melanoma is a comprehensive skin examination (IV, 2A). Thin melanomas (with Breslow thickness < 1 mm) are usually detected during a physical examination, but very rarely by the patient or family members. Thorough skin examination should be performed, if possible, during every outpatient visit or hospitalization. The principle is to assess full-body skin in good lighting, including difficult-to-reach areas (head, acral area — hands and feet, interdigital spaces, genitals and anal region, and mucous membranes).

Differential diagnosis

Medical conditions to be considered during differential diagnosis of early and locally advanced skin melanoma are presented in Table 2.

Table 2. Clinical differential diagnosis of cutaneous melanoma

Early skin melanoma
— Melanocytic naevus, including junctional melanocytic naevus and compound melanocytic naevus
— Blue naevus
— Simple lentigo
— Actinic/solar keratosis
— Superficial basal cell carcinoma
— Spitz naevus
— Tattoo
Locally advanced melanoma
— Seborrhoieic keraratosis/wart
— Dermatofibroma/fibrous histiocytoma
— Keratoacanthoma
— Pigmented basal cel carcinoma
— Hemangioma
— Venous extravasation
— Pyogenic granuloma/lobular capillary hemangioma
— Pigmentosus ebaceous cyst
— Kaposi sarcoma
— Glomus tumor
— Other appendicular tumors, particularly pigmentosus
— Onychomycosis
— Subungual or subcorneal hematoma

Dermoscopy (dermatoscopy)

The recommended test used in the initial, quick, and non-invasive diagnosis is dermoscopy (dermatoscopy) (II, A) [13, 14]. The examination consists of a visual assessment of all lesions on the patient's skin using a hand-held dermatoscope with either polarized or non-polarized light with immersion at 10-fold magnification [13, 14]. Dermoscopy improves diagnostic sensitivity by about 30%. The simplest principle of dermoscopic evaluation (the so-called Argenziano three-point checklist of dermoscopy) is based on the clinical suspicion of melanoma if two of the following three criteria are met: 1) asymmetric distribution of dermoscopic structures within the lesion, 2) atypical pigment network (APN), 3) blue-white veil. The sensitivity and specificity of this diagnostic method reach 96.3% and 94.2%, respectively. Other methods of dermoscopic analysis, including the ABCD dermoscopic method, pattern analysis, seven-point scale, Menzies method, or CASH (color, architecture, symmetry, homogeneity) algorithm, are characterized by comparable sensitivity with slightly greater specificity. It should be emphasized that these dermoscopic evaluation systems do not apply to lesions in "special locations" involving the skin of the face and acral region — palms and soles, and on the nail plate, on mucous membranes of the mouth and genitals. In such cases, it is necessary to use dermoscopic algorithms, developed separately based on characteristic features and dermoscopic patterns for the above specific locations. In the case of syndrome of atypical moles, it may be a useful practice to collect photographic documentation of selected lesions or the entire surface of the skin (total body photography) and to compare the photos taken and the observed skin lesions at successive time intervals. Some systems perform an automated comparison of dermoscopic images at successive time intervals, but they are not widely used due to technological limitations.

Initial dermoscopic diagnosis can be verified with reflectance confocal microscopy (RCM) as part of specialist dermatological advice. In justified cases, when an excisional biopsy is not possible (e.g. suspected melanoma in the area of extensive birthmarks in young children), it is possible to perform dermoscopy-guided biopsy and histopathological examination.

Histopathological diagnosis — excisional biopsy of the primary skin lesion (microstaging I)

Excisional biopsy of the primary skin lesion, clinically suspected of being malignant melanoma, is the procedure of choice as it provides microscopic confirmation of melanoma diagnosis and makes it possible to obtain information about the most important prognostic factors, which are used for further treatment planning (microstaging) (III, 2A) [1, 12, 15]. There are no indications for „prophylactic" excision of birthmarks that do not raise suspicion of skin melanoma.

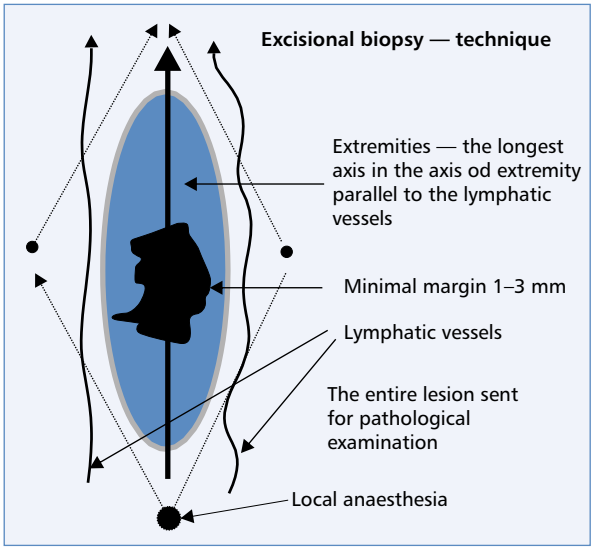

Figure 1. (According to W. Ruka) Recommended direction of the cut during the excisional biopsy. Spindle-shaped excision of the suspected pigmentary lesion should be made collaterally to the regional lymph vessel (toward the nearest draining lymph node/lymph vessel confluence), in the majority of cases enabling a primary suture of the wound

Excisional biopsy is a simple surgical procedure and is often possible to run outpatient. Excision of a suspected skin lesion is performed under local infiltration anesthesia with a lateral margin of 1–3 mm of unchanged skin. Apart from the entire thickness of the skin, the surgical preparation also contains a superficial layer of fatty tissue; the fascia is not cut out, and the wound is closed with a primary suture. The skin incision should be in line with the long axis of the body (Fig. 1), only facial skin should be cut in line with aesthetic lines. Transverse cuts (in the limb localization) should never be performed, as in case of reoperation, they result in a very bad cosmetic effect and are considered an error for oncological reasons.

The results of fine-needle or core-needle aspiration biopsy and incisional (section) or shave biopsy do not provide reliable information regarding primary melanoma in accordance with the requirements of the American Joint Cancer Committee/Union Internationale Contre le Cancer (AJCC/UICC) system, and these methods should not be used.

In the case of very large and ulcerated lesions, the sampling procedure can use imprint cytology, consisting in pressing the glass slide against the tumor surface and sending the collected material for cytological examination, a fine-needle or core-needle biopsy, as well as incisional biopsy (with taking a section from the lesion).

Histopathological diagnosis

Pathological examination of the material obtained by excision of the primary lesion consists of macro- and microscopic examination with the specification of mandatory and conditionally tested features, which should be included in a standardized histopathological report.

1. Macroscopic examination
   a. Size of removed skin fragment with the lesion (3 dimensions).
   b. Lesion size (2 dimensions).
   c. Color (uniform, non-uniform).
   d. Lesion border (regular, irregular).
   e. Nodule (present, absent).
   f. Margin (lateral, depth).
2. Microscopic examination of the skin with the lesion. Compulsory microscopic features:
   a. Histopathological diagnosis according to the World Health Organization (WHO) 2018 histopathological classification of melanocytic tumors and the ICD-O code.
   b. Breslow thickness in millimeters, measured from the granular layer of epidermis or ulcer bottom to the deepest infiltrating melanocyte nests.
   c. pT staging according to the 8th edition of AJCC/UICC 2017 pTNM classification [16].
   d. Presence or absence of a full-thickness ulcer resulting from melanoma cell penetration into the epidermis, other than a mechanical ulcer, and its extent determined by the diameter or percentage of affected skin area over the tumor.
   e. Number of division figures per 1 mm^2 (only in the vertical component, measured in the fields with the highest mitotic activity, the so-called hot spots).
   f. Growth phases (horizontal [radial] — intra-epidermal, *in situ* and sagittal [vertical], always invasive cutaneous).
   g. Presence or absence of microscopic satellite foci (foci from melanocytes over 0.05 mm in diameter at a distance of more than 0.3 mm and up to 2 cm from the invasive component of the primary melanoma — feature N).
   h. Peripheral margin (from *in situ* and invasive component) and in the depth.

Features conditionally determined in the histopathological report:

   a. Regression degree.
   b. Clark infiltration depth (level I, II, III, IV, V).
   c. Cell type (epithelioid, fusiform, small, pleomorphic, other).
   d. Presence and intensity of tumor-infiltrating lymphocytes (TILs) assessed only in the vertical component: absent, moderately abundant — TILs non-brisk, abundant — TILs brisk.

e. Presence or absence of lymphatic and blood vessels infiltration.
f. Presence or absence of nerve trunks infiltration.
g. Presence of nevus.

In selected cases, to confirm clinically occult metastases in sentinel lymph nodes and distant metastases, the differential diagnosis between benign and malignant melanocytic lesions should encompass immunohistochemical tests with antibody panel including HMB45, Melan A, p16, SOX-10, and Ki-67.

The WHO Classification of Skin Tumours, the 4th Edition 2018, distinguishes the following types of melanoma [17]:

— melanocytic tumors in intermittently sun-exposed skin;
  • superficial spreading melanoma, low-CSD melanoma;
— melanocytic tumors in chronically sun-exposed skin;
  • lentigo maligna melanoma,
  • desmoplastic melanoma;
— Spitz melanoma;
— acral melanoma;
— mucosal melanomas: genital, oral, sinonasal;
  • mucosal lentiginous melanoma,
  • mucosal nodular melanoma;
— melanoma arising in blue nevus;
— melanoma arising in giant congenital nevus;
— ocular melanocytic tumors;
  • uveal melanoma: epithelioid cell melanoma, spindle cell melanoma type A, spindle cell melanoma type B,
  • conjunctival melanoma;
— nodular melanoma;
— nevoid melanoma;
— metastatic melanoma.

Assessment of PD-L1 receptor expression, reported as a percentage of tumor positive cells, may be useful in patients with stage III or IV (I, 2B), although its clinical application is currently very limited [10].

Molecular diagnostics

Performing *BRAF* gene mutations testing (in formalin-fixed paraffin-embedded [FFPE] tissue specimens) is obligatory in patients with stage III (operable and inoperable) and stage IV (I, 1) melanoma [10] and recommended in stage IIC. However, mutation testing is not recommended in patients with stage I and IIA–IIB primary melanomas [10]. In the absence of *BRAF* gene mutation, *NRAS* and *KIT* genes mutations testing (II, 2B) should be considered [10]. There is no need for additional sampling from metastases to verify the presence of molecular abnormalities. Genetic testing should be performed in centers subject to quality control (QC). Laboratories should have two alternative methods to identify *BRAF* gene mutations at codon 600. The most commonly used tests are based on the qPCR method, which allows identifying the most common mutations in a relatively short time and with high sensitivity. The second method of *BRAF* gene mutation testing should allow for precise verification of codon 600 mutation type; in such cases, direct Sanger sequencing is used. It enables the identification of all variants occurring in exon 15 of *BRAF* gene (codon 600 region), including p.(Val600Glu), c. 1799T>A — V600E; as well as p.(Val600Glu), c.1799_1800delinsAA, V600E2; p.(Val600Lys), c.1798_1799GT>AA, V600K; p.(Val600Asp), c.1799_1800delinsAC, V600D; p.(Val600Asp), c.1799_1800delinsAT, V600D2; p.(Val600Gly), c.1799T>G, V600G; p.Val600Arg, c.1798_1799GT>AG, V600R; and p.Val600Met, c.1798G>A, V600M. This is of particular importance, considering that particular variants translate into different activities of BRAF protein kinase. For this reason, Sanger sequencing is also commonly used as a verification analysis after mutation detection using a qPCR-based assay. In general, qPCR tests do not distinguish between and not determine exactly which nucleotide (and consequently) amino acid is found in BRAF. It should be also mentioned that, unlike sequencing, qPCR testing is also dedicated to the identification of only selected V600 variants (not all). Therefore, in the case of using the qPCR test, which was dedicated to the identification of only selected V600 variants (not all) and *BRAF* mutation-negative status, it is recommended to perform direct sequencing to verify the result, especially when the clinical manifestation supports the presence of *BRAF* gene mutation.

An alternative to tissue sampling for *BRAF* mutation testing can be circulating tumor DNA (ctDNA) analysis. DNA secreted by cancer cells and slowly circulating in the patient's bloodstream can be obtained using dedicated blood sampling and collection kits, and this is the so-called liquid biopsy. Molecular biology techniques used to determine the V600 mutation in ctDNA must be characterized by high analytical sensitivity (dedicated qPCR and ddPCR kits). It should be emphasized, however, that ctDNA can be used to test *BRAF* mutation only when the tissue material is unavailable or is undiagnostic due to low quality [18, 19].

It is recommended to perform the diagnostics of mutations occurring in the promoter of *TERT* and *HRAS* genes to correctly classify melanocytic lesions of the spitzoid type, with particular emphasis on differentiation from melanoma in this group of melanocytic lesions [20, 21].

It is currently known that certain melanoma subtypes are associated with specific mutations: mutations in *BRAF*, *CDKN2A*, *NRAS,* and *TP53* genes — skin melanomas; in *NF1* and *KIT* genes — acral melanomas;

in *SF3B1* genes — mucosal melanomas; in *GNAQ*, *GNA11* genes — melanomas originating in the cellular blue nevus and the organ of sight [22].

In a small percentage of primary lesions, where the morphology and immunohistochemical testing do not allow for an unambiguous determination of the nosological status (entities belonging to the category of melanocytic lesions with an uncertain malignancy potential, sometimes also referred to as borderline lesions), it is possible to use molecular biology techniques to refine the diagnosis. According to the current recommendations in Europe and worldwide, the following tests can be used for this purpose: immunohistochemical staining, gene expression profiling (GEP), fluorescence *in situ* hybridization (FISH), comparative genomic hybridization (CGH), or next-generation sequencing (NGS).

Staging and prognostic factors

Clinical staging

The current TNM (tumor-node-metastasis) classification system for the clinical and pathological staging of skin melanoma comes from a revision presented in 2017 (Tab. 3) (II, 2A) [16].

The basis for the diagnosis of skin melanomas is the histopathological examination of the entire surgically resected pigmentary lesion. No other procedure, except excisional biopsy (the so-called microstaging I), allows for the correct diagnosis (III, 2A).

After a histopathological diagnosis of cutaneous melanoma is achieved, treatment should be initiated according to the stage (see below).

First of all, a thorough physical examination should be performed, including examination of the full-body skin (presence of other suspicious pigmented, satellite, and/or *in-transit* lesions), lymph nodes assessment, and examination for the presence of possible distant metastases. Imaging tests are not routinely required in low-stage primary lesion (pT1a) melanomas. However, in higher stages of T (T1b–pT4b), it is advisable to perform an ultrasound examination (US) of the regional lymph nodes before removing the scar with sentinel node biopsy. If there are any suspicious changes in the ultrasound examination, a biopsy with histological evaluation should always be performed. If there are no clinical symptoms, imaging tests such as chest, abdominal, pelvic computed tomography (CT) with contrast, positron emission tomography (PET-CT), and magnetic resonance imaging (MRI) of the brain are not recommended, although they may be considered at higher stages (pT3b and higher) (III, 2B) [10]. In the case of clinical metastases in inguinal lymph nodes, pelvic-abdominal CT or MRI with contrast is indicated.

In patients with lymph nodes or skin metastases of melanoma of unknown primary melanoma (UPM), it is necessary to carefully search for a possible primary tumor (especially on the scalp, mucous membranes) and to obtain detailed medical history (e.g. regarding previous lesions treated with ablative methods as part of aesthetic medicine or dermatosurgery). In such a clinical situation, it is advisable to perform additional imaging examinations (brain MRI, CT with contrast, or PET-CT of neck, chest, abdomen, and pelvis) (IV, 2B).

Laboratory tests are not routinely performed while, in stage IV, lactate dehydrogenase (LDH) level is measured.

Prognostic factors

Identification of clinical and pathomorphological prognostic factors aims at understanding the biology of the neoplasm and facilitating the planning of appropriate treatment for a given patient, taking into account the risk of disease recurrence and the probability of survival after treatment.

Primary melanoma

The most important prognostic factors in patients with non-metastatic skin melanomas include Breslow thickness and the presence of (micro) ulceration of the primary lesion. The prognostic significance of the number of infiltrated lymph nodes and microsatellites as a component of feature N was also found. These factors were used in the development of the TNM classification, version 8 (Tab. 3) [12, 15, 16, 23].

Metastasis in regional lymph nodes (stage III)

The presence of metastases in regional lymph nodes is the most important factor determining the prognosis in patients with skin melanomas. In the case of metastases, the most important factor is the number of metastatic regional lymph nodes. The type of metastasis is also an important factor — patients with clinically occult lymph nodes (neoplastic lesions detected during microscopic examination in a non-enlarged and clinically occult lymph node collected during sentinel nodes biopsy) have a better prognosis than patients with clinically detected lymph nodes (tumor lesions diagnosed in the microscopic examination of regional lymph nodes that are detected during physical examination or visible on imaging tests). An additional factor with a significant negative impact on the prognosis in patients with lymph node metastases is the presence of tumor infiltration beyond the lymph node capsule.

Metastases in distant organs (stage IV)

The most important prognostic factors in patients with extra-regional metastases are the location of the

Table 3. 2017 TNM AJCC/UICC melanoma staging

A. TNM System Categories

Feature T	Tumor Breslow thickness [mm]	(Micro-) ulceration
Tis (melanoma in situ)	Not applicable	Not applicable
Tx: Primary tumor thickness cannot be assessed (e.g. diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (e.g. unknown primary or completely regressed melanoma)	Not applicable	Not applicable
T1	≤ 1.0	Unknown or unspecified
T1a	< 0.8	Without ulceration
T1b	< 0.8	With ulceration
	0.8–1.0	With or without ulceration
T2	> 1.0–2.0	Unknown or undefined
T2a	> 1.0–2.0	Without ulceration
T2b	> 1.0–2.0	With ulceration
T3	> 2.0–4.0	Unknown or undefined
T3a	> 2.0–4.0	Without ulceration
T3b	> 2.0–4.0	With ulceration
T4	> 4.0	Unknown or undefined
T4a	> 4.0	Without ulceration
T4b	> 4.0	With ulceration
Feature N	**Number of regional lymph nodes with metastases**	**Presence of *in-transit*, satellite, and/or microsatellite metastases**
Nx	Regional nodes not assessed (e.g. SLN biopsy not performed, regional nodes previously removed for another reason) Exception: When there are no clinically detected regional metastases in a pT1 cM0 melanoma, assign cN0 instead of pNX	No
N0	No regional metastases detected	No
N1	1 tumor-involved node or *in-transit*, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	1 clinically occult (i.e. detected by SLNB)	No
N1b	1 clinically detected	No
N1c	No regional lymph node disease	Yes
N2	2 or 3 tumor-involved nodes or *in-transit*, satellite, and/or microsatellite metastases with 1 tumor-involved node	
N2a	2 or 3 clinically occult (i.e. detected by SLNB)	No
N2b	2 or 3, at least 1 of which was clinically detected	No
N2c	1 clinically occult or clinically detected	Yes
N3	≥ 4 tumor-involved nodes or *in-transit*, satellite, and/or microsatellite metastases with ≥ 2 tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	≥ 4 clinically occult (i.e. detected by SLNB)	No
N3b	≥ 4, at least 1 of which was clinically detected, or presence of any number of matted nodes	No
N3c	≥ 2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

→

Table 3 (cont.). Clinical staging classification according to TNM AJCC/UICC from the year 2017

Feature M	Location of metastases	LDH serum activity
M0	No distant metastases	
M1a	Distant metastasis to skin, soft tissue including muscles, and/or nonregional lymph node	Not recorded or unspecified
M1a (0)		Not elevated
M1a (1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b (0)		Not elevated
M1b (1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c (0)		Not elevated
M1c (1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d (0)		Not elevated
M1d (1)		Elevated

*Micro/satellitosis — tumor or nodular infiltration (macro- or microscopically) up to 2 cm from the primary lesion of skin melanoma; *in-transit* — metastases in the skin or subcutaneous tissue more than 2 cm from the primary lesion of skin melanoma to the level of the nearest regional lymph nodes; LDH — lactate dehydrogenase; SLB — sentinel lymph node biopsy

B. Stages category

Clinical stages *				Pathological stages**			
	T	N	M		T	N	M
0	Tis	N0	M0		Tis	N0	M0
IA	T1a	N0	M0		T1a	N0	M0
					T1b	N0	M0
IB	T1b	N0	M0		T2a	N0	M0
	T2a	N0	M0				
IIA	T2b	N0	M0		T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0		T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0		T4b	N0	M0
III***	Any T	N1	M0				
		N2					
		N3					
				IIIA	T1a/b–T2a	N1a	M0
						N2a	M0
				IIIB	T0	N1b/N1c	M0
					T1a/b-T2a	N1b/c lub N2b	M0
					T2b/T3a	N1a–N2b	M0
				IIIC	T0	N2b, N2c	M0
						N3b lub N3c	M0
					T1a–T3a	N2c lub N3a/b/c	M0
					T3b/T4a	Każdy N ≥ N1	M0
					T4b	N1a–N2c	
				IIID	T4b	N3a/b/c	M0
IV	Any T	Any N	AnyM1		Any T	Any N	AnyM1

*Clinical staging includes primary microstaging and clinical/radiological/histopathological assessment of the presence of metastases. For this reason, in principle, it can only be used after complete excision of the primary skin melanoma (excisional biopsy) and assessment of the presence of metastases in the surrounding lymph nodes and distant organs;

**Pathological staging includes primary microstructure and pathological evaluation of lymph nodes within regional runoff: after sentinel lymph node biopsy or radical lymphadenectomy (except for stages 0 and IA -pTis/pT1 cN0 cM0, where no surgery is performed on regional lymph nodes);

***There are no stage III subgroups in clinical staging

metastases and LDH level. Patients with central nervous system (CNS) metastases have the worst prognosis in this group.

Treatment

Principles of primary lesion treatment and surgical evaluation of regional lymph nodes

Surgical treatment after excisional biopsy

Surgery is the treatment of choice in patients with melanoma (I, 1). After an excisional biopsy of suspicious pigmented lesion — when the cutaneous melanoma is diagnosed, a decision should be made on a possible radical excision of the scar with appropriate margins and a sentinel lymph node biopsy (Fig. 2).

Radical treatment of the primary melanoma covers radical excision of scar after the excisional biopsy of the primary lesion.

Based on the results of six randomized multicenter studies, extensive (i.e., with margin ≥ 3 cm) excision of was abandoned in favor of narrower margins of healthy tissues resected. The following margins during radical excision of primary melanoma lesions are currently recommended (excision of scar after excisional biopsy of the primary lesion): melanoma *in situ* — 5 mm margin, melanoma with Breslow thickness ≤ 2 mm — 1 cm, melanoma with Breslow thickness > 2 mm — 2 cm (Tab. 4) (I, 1).

Using a margin greater than 2 cm reduces the local recurrence rate but does not improve long-term survival. A scar after excisional biopsy of melanoma with Breslow thickness of ≤ 2 mm should be removed without the superficial fascia; however, for a scar after biopsy of melanoma with a thicker infiltration and appropriate margin at the bottom, the fascia may be also removed. These rules do not apply to melanoma localized on facial skin, where there is no fascia, and resection margins may be narrower. Some anatomical locations may require smaller margins of radical resection of primary melanoma; however, in the case of invasive melanomas, a minimum margin of 1 cm should be pursued. In the case of subungual localization of melanomas, the distal phalanx should be amputated.

Sentinel node biopsy (microstaging II)

The following patients are eligible for a sentinel lymph node biopsy (I, 1) [1, 12, 24, 25]:

— after excisional biopsy with a diagnosis of skin melanoma confirmed by histopathological examination, but not after wide excision of the primary lesion;
— with Breslow infiltration thickness ≥ 0.8 mm or with (micro) ulceration on melanoma surface, regardless of the thickness (melanoma with the primary lesion classified as pT1b-T4b according to the TNM AJCC/UICC 2017 classification); according to the data of the American Society of Surgical Oncology (SSO), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO) [26], a sentinel lymph node biopsy may be considered for melanomas with Breslow thickness 0.8–1.0 mm in the pT1b stage with additional unfavorable prognostic factors, such as, for example, the mitotic index ≥ 1/mm^2) (II, 2A);
— without clinical signs of metastases in regional lymph nodes and distant organs.

Sentinel node biopsy is an essential method of assessing the presence of micrometastases in the lymph nodes [23].

When performing a sentinel lymph node biopsy, preoperative lymphoscintigraphy and intraoperative lymphoscintigraphy combined with staining should be used. A sentinel node biopsy should be performed after excisional biopsy, simultaneously with radical resection of the scar. The available data do not indicate a negative prognostic impact of the sentinel lymph node biopsy performed 6 weeks after resection of the primary lesion (III, B). The accuracy of the method depends on the cooperation of nuclear medicine specialists, surgeons, and pathologists. Sentinel lymph node biopsy is a „minimally invasive" diagnostic method due to low early and late postoperative complications rates.

All lymph nodes found should undergo pathological examination. It is sufficient to collect one section from the lymph nodes containing overt clinical melanoma metastases (macroscopically visible metastatic deposits). In cases of sentinel lymph nodes examination, aimed at confirmation or exclusion of clinically occult melanoma metastases, serial sections of the entire lymph node should be performed with slices every 2–4 mm and an immunohistochemical examination of melanoma-specific markers such as HMB45, Melan-A, S-100, and SOX-X. The histopathological report describing this material should include 1) the number of lymph nodes found, 2) the number of lymph nodes containing metastases, 3) the size and location of the largest metastatic site, 4) the presence (or absence) of the spread of metastasis beyond the nodal capsule, and 5) the presence of tumor cell embolism in the vessels.

The results of the prospective Multicenter Selective Lymphadenectomy Trial 1 (MSLT-1) indicate that sentinel lymph node biopsy in melanoma patients allows identifying the groups of patients at high risk of neoplastic spreading, helps proper staging, provides excellent regional control, and allows for the qualification of patients for clinical trials according to the same criteria [24]. In the MSLT-1 study, no improvement in relapse-free survival and overall survival in the full study population subjected to sentinel lymph node biopsy was shown compared to the group with follow-up alone. However, in the subgroup of patients with current lymph

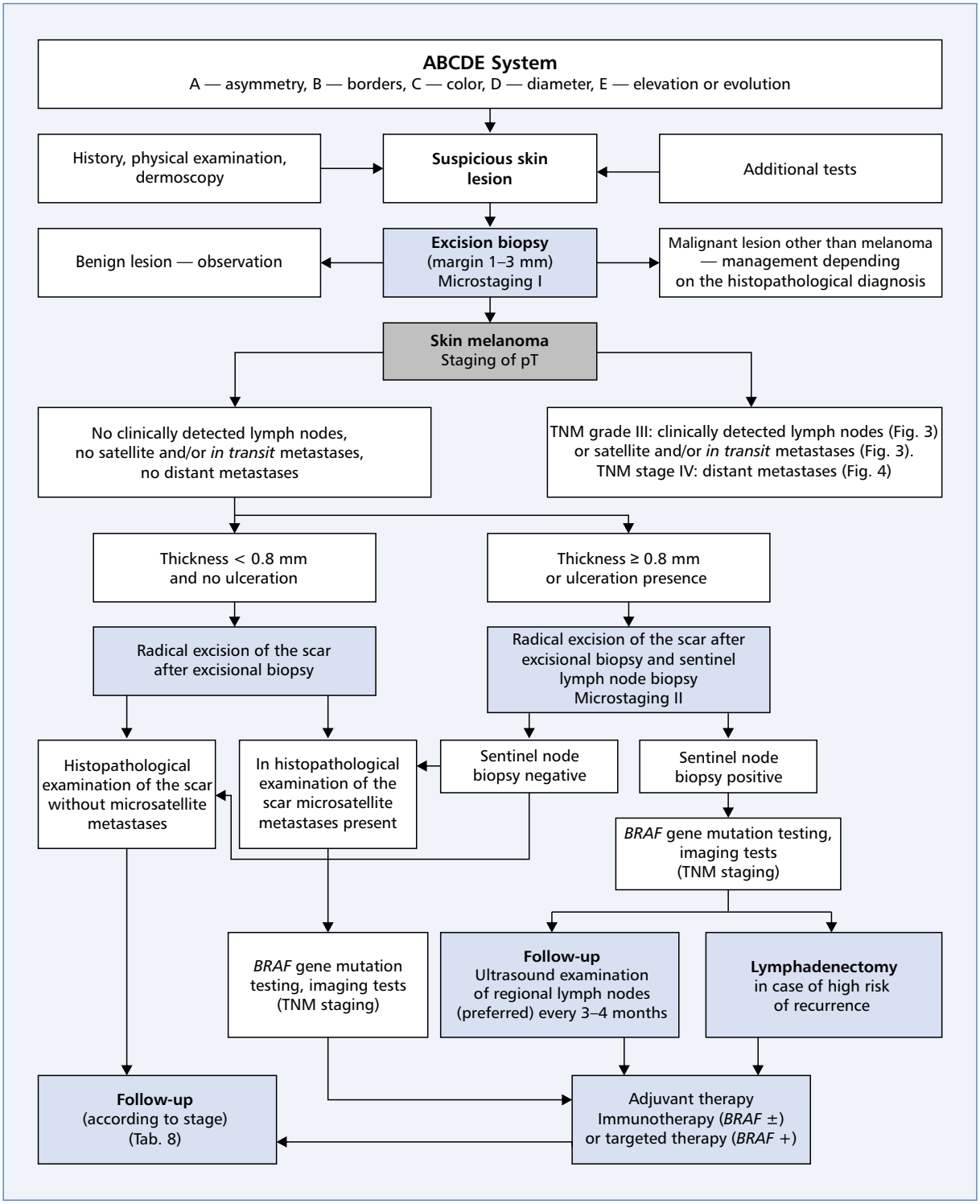

Figure 2. Algorithm for diagnosis and therapy in cutaneous melanoma; FNB — fine needle aspiration biopsy; TNM tumor-node-metastases stage classification

node metastases, 10-year survival was significantly better in patients who underwent immediate lymphadenectomy in the case of diagnosed sentinel lymph node metastasis compared to patients who underwent such treatment later due to the detection of clinically detected metastases (62.1% *vs.* 41.5%; p = 0.006) [24].

Table 4. Summary of recommendations of the National Comprehensive Cancer Network (NCCN) v. 1.2021, the European Organization for Research and Treatment of Cancer (EORTC) and the European Society of Medical Oncology (ESMO) regarding the final margin of radical resection of primary skin melanoma depending on its thickness according to the Breslow scale

Melanoma thickness (according to the Breslow scale)	Recommended clinical margin
In situ	0.5 cm
≤ 2.0 mm	1 cm
> 2.0 mm	2 cm

Radiotherapy

Independent RTH with a radical (non-palliative) intention can only be used in the case of an extensive lentigo malign melanoma (LMM) type lesion.

Palliative radiotherapy can be used in inselected indications as in the case of primary or metastatic lesions that do not respond to systemic treatment.

Treatment of metastases in regional lymph nodes

Treatment after positive sentinel lymph node

After histopathological confirmation of melanoma metastases in sentinel lymph nodes:

a. the patient can be left under close observation provided that ultrasound examinations of the lymphatic drainage are performed every 3–4 months (the preferred approach) or,
b. radical lymphadenectomy, the so-called completion lymph node dissection (CLND), may be considered because, in the remaining lymph nodes (non-sentinel lymph node), melanoma metastases are found using routine histopathological methods in about 20% of patients [27] (especially with the size of micrometastases > 1 mm).

The results of two published randomized clinical trials (RCTs) [28, 29], one of which had insufficient statistical power [29], showed no improvement in melanoma-dependent overall survival in patients undergoing CLND [28] and in distant-metastasis-free survival [29], but disease-free survival was longer in patients undergoing CLND (fewer relapses in the nodal area). At the same time, the basic prognostic significance of sentinel lymph node biopsy was confirmed in these studies (I, 1). It should also be noted that the stage after CLND changed only in about 6% of patients. Currently, CLND is performed in clinical practice only in patients with a very high risk of metastases in non-sentinel lymph nodes, such as large size of the sentinel lymph node metastasis, metastases in more than 2 sentinel lymph nodes, or extra-capsular infiltration of the sentinel lymph node [25, 30].

Before deciding on major local surgery, staging must include high-resolution imaging techniques such as PET-CT, CT, or MRI to rule out distant metastases (III, 2A).

Treatment in the presence of metastases in clinically detected regional lymph nodes

Clinically detected metastases in regional lymph nodes are lesions detected by physical examination or imaging studies (in the 7th edition of the AJCC classification, this feature was referred to as macroscopically visible lymph node metastases). If melanoma metastasis in clinically detected regional lymph nodes is confirmed by fine-needle aspiration biopsy or by histopathological examination, lymphadenectomy should be performed in the area of regional lymphatic drainage.

When qualifying patients for lymphadenectomy, clinical examination and imaging tests should be used. Detailed imaging examinations using PET-CT, CT (especially of the pelvis when metastases in the iliac or obturator lymph nodes are suspected), or MRI should be performed to exclude the presence of distant metastases. Imaging examination to exclude brain metastases is always performed in the case of clinical symptoms and stage IIIC.

Patients with skin melanomas with metastases in regional lymph nodes constitute a group with a very different prognosis (5-year survival rate of 15–70%). Prospective clinical trials have not confirmed the benefits of elective lymphadenectomy in patients without clinical evidence of melanoma metastases in the lymph nodes. Currently, lymphadenectomy in patients with skin melanomas is performed only when metastases are found in tissue sampled by fine-needle biopsy (and surgical biopsy in special cases) from enlarged and clinically suspicious lymph nodes or, in some cases, after confirmation of the presence of metastasis in sentinel lymph nodes in clinically unsuspected lymphatic drainage region (microstaging II — see above) [1, 24, 31] (Fig. 3).

Therapeutic lymphadenectomy

The extent of the therapeutic lymphadenectomy in cutaneous melanomas is as follows (III, 2A):

— in axillary dissection, all lymph nodes should be removed in accordance with the anatomical definition (3 groups of lymph nodes together with surrounding fascia: lower level — paramammary and subscapular lymph nodes, middle level — middle axillary lymph nodes, upper level — axillary and subclavian vein lymph nodes);
— in inguinal dissection, the lymph nodes in the inguinofemoral area, lying below the inguinal ligament in the femoral triangle, along with fascia of thigh muscles, femoral lymph nodes along the external iliac vessels (possibly also internal and common), and the obturator lymph nodes in the case of diagnosed

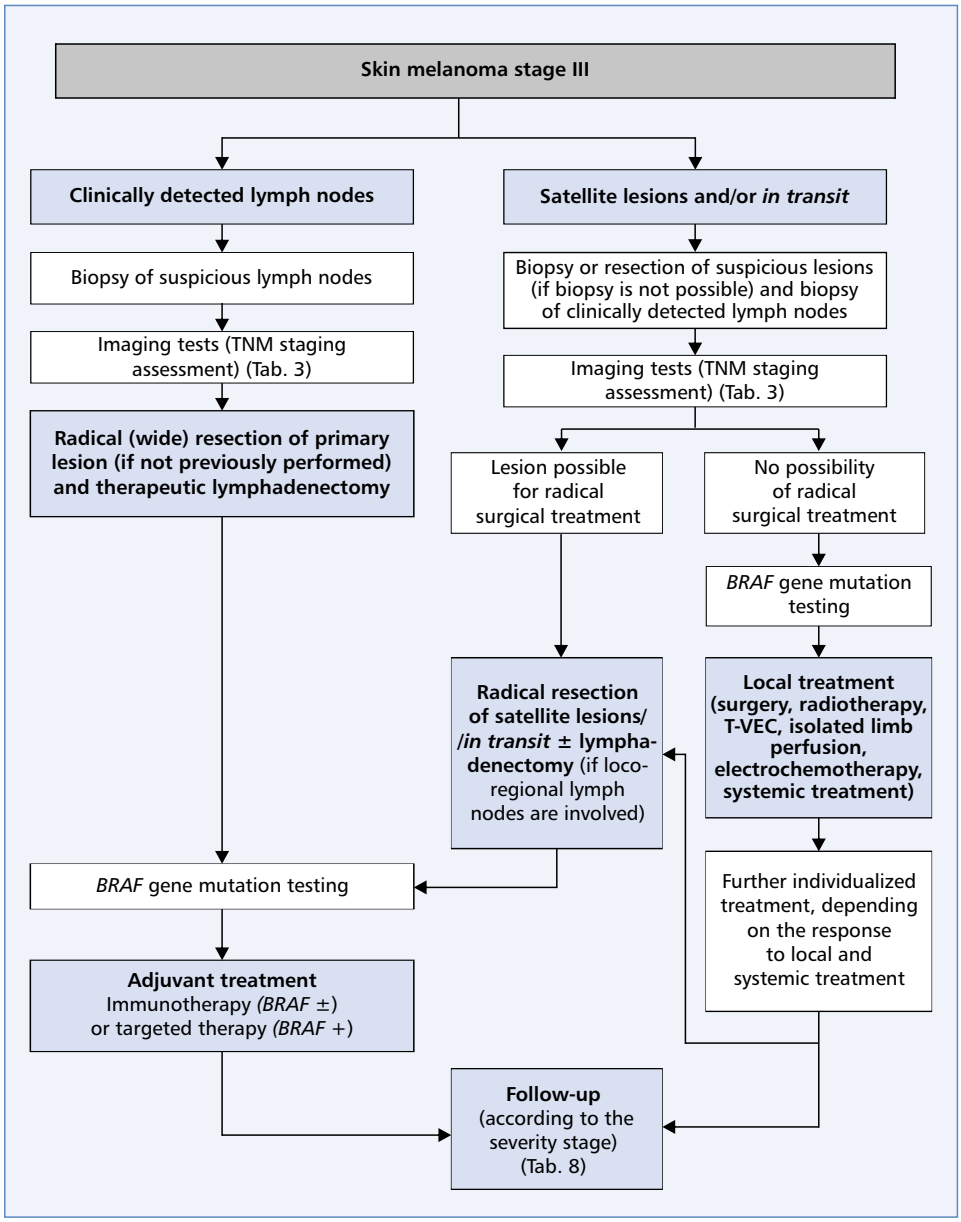

Figure 3. Skin melanoma stage III (metastases detected clinically or in imaging tests)

metastases in sentinel nodes), lymphadenectomy should be limited only to inguinal lymph node;

— in cervical dissection, modified operations can be performed that meet the requirement of maximal radicality, with the removal of neck structures containing superficial (anterior and posterior) and deep lymph nodes *en bloc*, limited from the back by the deep cervical fascia, and from the front by platysma muscle.

In some cases, it is necessary to perform a lymphadenectomy in the popliteal or elbow fossa.

In the case of isolated metastases of melanoma with an unknown primary, the same principles of surgical and systemic treatment are applied [32].

Satellite lesions, *in-transit* metastases, and local recurrence

The terms satellitosis (microscopic and macroscopic), *in-transit* metastasis, and local recurrence are a continuum and represent different forms of the same pathological phenomenon. Satellitosis is defined as neoplastic infiltration or nodules (macro- or microscopic) in the skin or subcutaneous tissue within 2 cm of the primary melanoma, while *in-transit* metastases are neoplastic lesions in the skin or subcutaneous tissue more than 2 cm from the primary skin melanoma to the level of the nearest regional lymph runoff. Local recurrence, on the other hand, which often occurs even after very wide resection

of the primary lesion) usually represents the spread of melanomas through the surrounding lymphatic vessels; microsatellites become macrosatellites and then may transform into *in-transit* metastases. For this reason, in most studies the mentioned forms of recurrent melanoma are analyzed together and show a similar prognosis (10-year survival rate of 20–30%).

Surgery is the primary method of local treatment of local recurrence and *in-transit* metastases. Decision whether to operate should be individualised and surgeons should consider the number, size, and location of lesions, as well as the clinical course (III, 2A). In the case of *in-transit* metastases, surgical treatment involves resection of countable lesions (< 10) with a microscopic margin free of melanoma infiltration (macroscopically it may be narrow). After resection, the patient should be qualified for systemic adjuvant treatment (II, B). In the case of single recurrent lesions, another sentinel lymph node biopsy may be considered. Resection should not be performed in the case of spread of *in-transit* skin melanomas. In multiple/unresectable lesions, local treatment methods (ablation, radiotherapy, cryotherapy), intratumoral immunotherapy (talimogen laherparepvec — T-VEC, PV-10 or interleukin 22 — not reimbursed) or local treatment (imiquimod not registered for this indication), electrochemotherapy (procedure reimbursed in Poland) (II, 2A), or systemic treatment may be considered. In the case of extensive, multiple lesions located on the limb, the preferred method is hyperthermic isolated limb perfusion (HILP), most often with melphalan, which can only be used in centers with appropriate equipment and experienced team (individual reimbursement decisions); the inability to use HILP is an indication for systemic treatment [1, 12, 15, 31, 33, 34].

Melanomas located within the mucous membranes

The clinical stage of mucosal melanoma is defined depending on the location of the primary lesion. However, the simplified staging system originally developed for head and neck melanomas can be used in all mucosal melanomas [35]. It consists of three stages:

— stage I — locally advanced tumor;
— stage II — regional lymph nodes involvement;
— stage III — distant metastases.

Regardless of the primary location, the primary treatment is radical surgical resection within healthy tissue margins (IV, 2A); recommended surgical margins have not been identified [36].

Melanomas of head and neck mucous membranes are very rare neoplasms with an aggressive course and poor prognosis. In 70–80% of cases, they develop in the nasal cavity and paranasal sinuses, and the oral cavity in the majority of remaining cases. It should be noted that the disease stage (TNM) is defined differently than in cutaneous melanomas (Tab. 5) [37]. Data on the treatment of mucosal melanomas located in mucous membranes of the head and neck region are limited. Surgery is the treatment of choice in stages T3, N0-1, and T4a, N0-1. For stage T4b, surgery is not recommended, and management should be led by multidisciplinary teams. In the case of involvement of the cervical lymph nodes, the recommended treatment is cervical lymphadenectomy followed by radiotherapy. Postoperative radiotherapy of the primary focus improves locoregional disease control and is recommended in most cases [38]. In melanomas located in the area of the anus/rectum, there was no benefit from abdominoperineal resection if local resection was possible (III, 2A) [36, 39–42]. Radical abdominoperineal resection (APR) with resection of the rectum may be justified in the following clinical situations:

— if wide local resection would result in impairment of anal function;
— if mesenteric lymph nodes are involved (without metastases in other organs);
— if it is impossible to perform resection with an R0 margin without performing a rectal resection;
— in the case of emergency surgery if the pathological examination reveals R1 margins or local recurrence.

Complementary radiotherapy is used on general principles in the case of non-radical resection revealed in microscopic evaluation [43]. In some locations, like anal or vulvar melanomas, sentinel lymph node biopsy is recommended (III, 2B).

Adjuvant therapy

Adjuvant therapy after surgical treatment is currently the standard of care. The primary and obligatory rule should be multidisciplinary team management with members having experience in the diagnosis and treatment of melanomas.

Adjuvant systemic therapy can be used after positive sentinel lymph node biopsy without the need for adjuvant lymphadenectomy. Treatment is available in Poland under the current B.59 drug program. The most important studies on the adjuvant treatment in melanoma patients at high risk of recurrence are summarized in the Table 6.

Currently registered agents for systemic (one-year) adjuvant treatment in clinical practice in patients after radical resection of stage III metastases (lymph node or *in-transit* metastases/satellitosis) include dabrafenib with trametinib (only patients with *BRAF* mutation), pembrolizumab and nivolumab (the latter also after metastasectomy in stage IV). The published results of clinical trials show an improvement in relapse-free survival, both as a result of adjuvant immunotherapy with immune checkpoint inhibitors and combined therapy with BRAF and MEK inhibitors (only in patients with a *BRAF* gene mutation) (I, 1).

Table 5. The American Joint Committee on Cancer (AJCC) TNM Staging System for Mucosal Melanoma of the Head and Neck (8th ed., 2017)

Primary tumor (T)	
T3	Tumors limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; for example: polypoid nasal disease, pigmented or nonpigmented lesions of the oral cavity, pharynx, or larynx
T4	Moderately advanced or very advanced
T4a	Moderately advanced disease Tumor involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease Tumor involvingthe the brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present
Distant metastases (M)	
M0	No distant metastases
M1	Distant metastases present

Table 6. Summary of the most important studies on adjuvant therapy in melanoma patients at high risk of recurrence

Study	**COMBI-AD** **dabrafenib + trametinib *vs.* placebo**	**Checkmate 238** **nivolumab *vs.* ipilimumab**	**EORTC 1325/Keynote 054** **pembrolizumab *vs.* placebo**
Author	Long 2017 Hauschild 2018	Weber 2017 Ascierto 2020	Eggermont 2018 Eggermont 2020
Study population	IIIA (> 1 mm), IIIB, IIIC	IIIB, IIIC, IV	IIIA (> 1 mm), IIIB, IIIC
BRAF gene mutations	100%	41%/43%	44%/43%
RFS	67% *vs*. 44% (2-year); HR 0.47 58% *vs*. 39% (3-year) 54% *vs*. 38% (4-year); HR 0.49 52% *vs*. 36% (5-year);	66% *vs*. 53% (18-month); HR 0.66 62.6% *vs*. 50.2% (24-month); HR 0.65 58% *vs*. 45% (36-month) 52% *vs*. 41% (48-month); HR 0.68	HR 0.57%; 18-month difference 18.2%: 71.4% *vs*. 53.2% 36-month difference 20% 64% *vs.* 44%
OS	91% *vs*. 83% (2-year) 86% vs. 77% (3-year); HR 0.57	78% *vs.* 77% (4-year)	NA

NA — not available; OS — overall survival; RFS — relapse-free survival

Radiotherapy as an adjuvant treatment can only be considered in individual cases and is not recommended as standard of care (II, 1).

There are ongoing studies on the use of systemic preoperative (neoadjuvant) treatment in patients with melanomas with clinical locoregional metastases.

Immunotherapy

Interferon alfa-2b

Based on a positive result from one of three Eastern Cooperative Oncology Group (ECOG) studies — ECOG 1684, high-dose interferon alfa-2b (IFN--alfa-2b) has been approved in the US and European Union for the treatment of patients with stage IIB-III melanoma, while in low doses only in Europe for stage II patients [44, 45]. The basis for registration was statistically significant prolongation of overall survival during approx. 7 years of follow-up, which was not confirmed in long-term observation (12 years). The results of the studies show a reproducible (10 out of 17 evaluated studies) improvement in disease-free survival, with recent meta-analyses showing a statistically significant reduction in the relative risk of relapse by 17–18% after

adjuvant therapy with IFN alfa-2b. The evidence for the overall survival improvement is much weaker and comes mainly from meta-analyses, and points to an improvement in 5-year overall survival by approx. 3–5% in the entire group of patients. Due to the controversial importance of adjuvant therapy with IFN alfa-2b in patients with intermediate and high-risk melanomas and its toxicity, the use of the drug should be individualized (II, 2B). The results of meta-analyses indicate that benefits of adjuvant IFN alfa-2b therapy may be observed in patients with ulcerated primary melanoma, especially in the subgroup with micrometastases (in the sentinel lymph node but without macrometastases of clinically enlarged lymph nodes) (I, 2B) [46, 47]. Interferon is not reimbursed in Poland as an adjuvant treatment and is less effective than other drugs currently used in adjuvant treatment.

Ipilimumab

In the United States, ipilimumab (anti-CTLA-4 antibody) is approved for adjuvant treatment of melanoma patients after lymphadenectomy due to regional lymph nodes metastases. A randomized study [48] showed a statistically significant improvement of relapse-free and overall survival after the use of ipilimumab, albeit at the cost of high toxicity of this therapy (II, 2B) [49]. Ipilimumab is not registered for adjuvant treatment in Poland.

Nivolumab

Nivolumab (anti-PD-1 antibody) showed a 10% improvement in relapse-free survival after one year compared to ipilimumab with less toxicity (I, 1) in a randomized clinical trial in patients with stage IIIB, IIIC, and stage IV (metastatic). It is currently registered and reimbursed for this indication [48]. Updated data, after longer follow-up, confirm the efficacy of one year adjuvant nivolumab treatment, regardless of the PD-L1 expression level and *BRAF* mutation status in relation to RFS (HR 0.66) and DMFS (HR 0.76) [50]. The 3-year relapse-free survival rate was 58% and was over 10% better than for ipilimumab. The results of the 4-year observations are similar.

Pembrolizumab

The results of the Keynote-054/EORTC 1325 study with 1019 patients also showed a reduction in the risk of disease recurrence (HR for RFS 0.57) and DMFS after one-year adjuvant treatment with pembrolizumab compared to placebo in the higher-risk group with stage III resectable disease (stage IIIA with micrometastases > 1 mm, IIIB and IIIC) (I, 1) [51, 52]. The RFS rate after 3.5 years of follow-up was 59.8% in the pembrolizumab group compared with 41.4% for the placebo group [53]. Pembrolizumab is associated with longer recurrence-free survival than placebo with 5-year rate of recurrence-free survival of 55.4%, hazard ratio for recurrence or death of 0.61 as well as 5-year rate of distant metastasis-free survival, of 60.6% and hazard ratio for distant metastasis or death of 0.62 [54].

Pembrolizumab as adjuvant therapy for up to approximately 1 year in stage IIB or IIC melanoma significantly improved relapse-free survival and it is currently approved in this indication, but not reimbursed in Poland (II, 2A) [55].

Other immunological drugs

Other methods of immunotherapy (e.g. interleukin 2), anti-melanoma vaccines, or cytotoxic drugs are of no use in adjuvant postoperative therapy.

Molecularly targeted therapy

Dabrafenib with trametinib

The use of one-year adjuvant treatment with dabrafenib with trametinib in patients with stage III, *BRAF*-positive, high-risk melanoma (stage IIIA with metastasis > 1 mm, IIIB/III C) showed an improvement in relapse-free and overall survival compared to placebo (I, 1) [56, 57]. Updated data from a 4-year follow-up confirm the benefit of treatment with dabrafenib and trametinib (RFS: 54%; HR: 0.49; DFS: 67%; HR: 0.53) [57]. In addition, a model was also presented to evaluate the percentage of additionally cured patients after the adjuvant treatment (cure rate), which accounts for as much as 17%. After 5-year follow-up, the percentage of patients without relapse was 52% in the group treated with dabrafenib with trametinib compared to 36% in the placebo group [58].

Adjuvant radiotherapy

In selected cases, after surgical treatment of high-risk melanomas, supplementary radiotherapy (RTH) is recommended — the dosing regimen includes hypofractionation of 3–8 Gy/fraction or conventional fractionation depending on the location. Indications for adjuvant RTH after primary tumor resection include the diagnosis of desmoplastic melanoma resected with narrow margins, presence of „positive" surgical margins (especially after resection of local recurrence), the presence of satellite foci, and increased neurotropism.

In the case of resection of local recurrence and lymphadenectomy due to metastases in regional lymph nodes, indications for supplementary RTH may include the presence of extracapsular lymph node infiltration, involvement of ≥ 4 lymph nodes (stage IIIC), diameter of the metastasis > 3 cm, detection of metastases in cervical lymph nodes (2 or more metastatic lymph nodes or metastasis of at least 2 cm), recurrence after resection [59, 60].

The results of the only completed randomized study, which assessed the value of adjuvant RTH (48 Gy in 20 fractions) after lymphadenectomy in patients at high risk of recurrence, confirmed the improvement of local control after irradiation, without affecting overall survival and increasing long-term locoregional complications and deterioration of patients' quality of life. This means that the use of adjuvant RTH should be limited (II, 2A) [61]. Adjuvant RTH after CLND should not be used.

Treatment of metastatic patients

The results of treatment of stage IV skin melanomas are still unsatisfactory. Currently, median overall survival exceeds 12–24 months, but 5-year survival is chieved by approx. 20–40% of patients.

The factors of significant prognostic importance in patients with stage IV melanoma are the performance status [performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale], LDH activity, and location of metastatic lesions. If the patient is eligible for surgical treatment or systemic treatment in stage IV, the disease stage should be assessed with imaging (CT with contrast or PET-CT of the chest, abdominal cavity, and pelvis; brain MRI with contrast) [1].

In the case of secondary lesions on the skin, in soft tissues, or extra-regional lymph nodes (M1a; better prognosis), the possibility of surgical resection should always be considered — the same should be done in the case of isolated (although not necessarily single) metastases to parenchymal organs, and then a decision regarding patient qualification for adjuvant treatment with nivolumab should be made (I, 1). In the case of metastatic lesions that cannot be resected, the choice of treatment depends on the presence of metastases in the central nervous system, which requires, first of all, consideration (the decision depends on the location and number of lesions) of neurosurgical treatment and/or irradiation of the central nervous system (usually stereotaxic or radiosurgery [62]) to delay the onset of bleeding or neurological disorders. Irradiation of CNS lesions may also be part of combination therapy during immunotherapy (preferred) or BRAF protein-targeted therapy (II, 2B). There is no indication for whole brain radiotherapy (WBRT) as adjuvant treatment after local treatment of melanoma metastases in CNS, as it does not improve outcomes. Detailed recommendations for the management of melanoma CNS metastases have been published [63].

In palliative care, RTH is also used in patients with metastases in soft tissues (for ulceration and pain) and bones (for pain control).

Progress in the treatment of metastatic melanoma, with low efficacy of classic cytotoxic drugs, is associated with 1) non-specific immunotherapy with anti-CTLA4 (ipilimumab) or anti-PD1 (nivolumab, pembrolizumab) monoclonal antibodies inhibiting systemic immunosuppressive mechanisms to induce antitumor response (activation of T lymphocytes) and 2) targeted therapy with serine-threonine kinase inhibitors (dabrafenib with trametinib, vemurafenib with cobimetinib or encorafenib with binimetinib) (I, A). Treatment with the above-mentioned drugs is reimbursed in Poland under the B.59 drug reimbursment program. Systemic treatment should be performed in centers that provide full range of therapeutic options [64]. The qualification of patients with metastatic melanoma for prospective clinical trials should still be considered (Fig. 4, Tab. 7).

Chemotherapy

Dacarbazine is the only cytotoxic drug registered in disseminated melanoma, and its effectiveness is limited (the objective response rate is 15%, median response duration is 4 months) [1]. The only approved regimen of dacarbazine use is the administration of the drug for 5 consecutive days at a daily dose of 200 mg/m^2; the possibility of a 1-day use of the drug at a higher dose (850–1000 mg/m^2 every 3 weeks) has not been formally approved, although it is a useful treatment in clinical practice. Paclitaxel alone or in combination with carboplatin does not substantially prolong response duration to second-line treatment. Randomized studies did not confirm the greater efficacy of multidrug chemoregimens using dacarbazine in combination with cisplatin, vinca alkaloids (e.g. vinblastine), and nitrosourea derivatives (e.g. carmustine), and tamoxifen.

Immunotherapy

Anti-CTLA-4 antibodies (ipilimumab)

Ipilimumab has been approved for the treatment of patients with disseminated melanomas and compared to gp100 peptide vaccine in second-line showed a statistically significant increase in median overall survival (difference of about 3.5 months) without a significant impact on the progression-free survival [65, 66]. The kinetics and response duration for ipilimumab are different than in classic chemotherapy — the benefit of treatment is observed only after 3–4 months, which limits its use to patients with advanced melanoma with minimal symptoms, good performance status and slow disease course, and (due to safety profile) without accompanying autoimmune diseases. Due to the late occurrence of objective responses, a conclusive assessment of the effectiveness of ipilimumab should be made 12 weeks after the treatment commencement, especially considering the possibility of paradoxical progression (pseudoprogression) related to infiltration

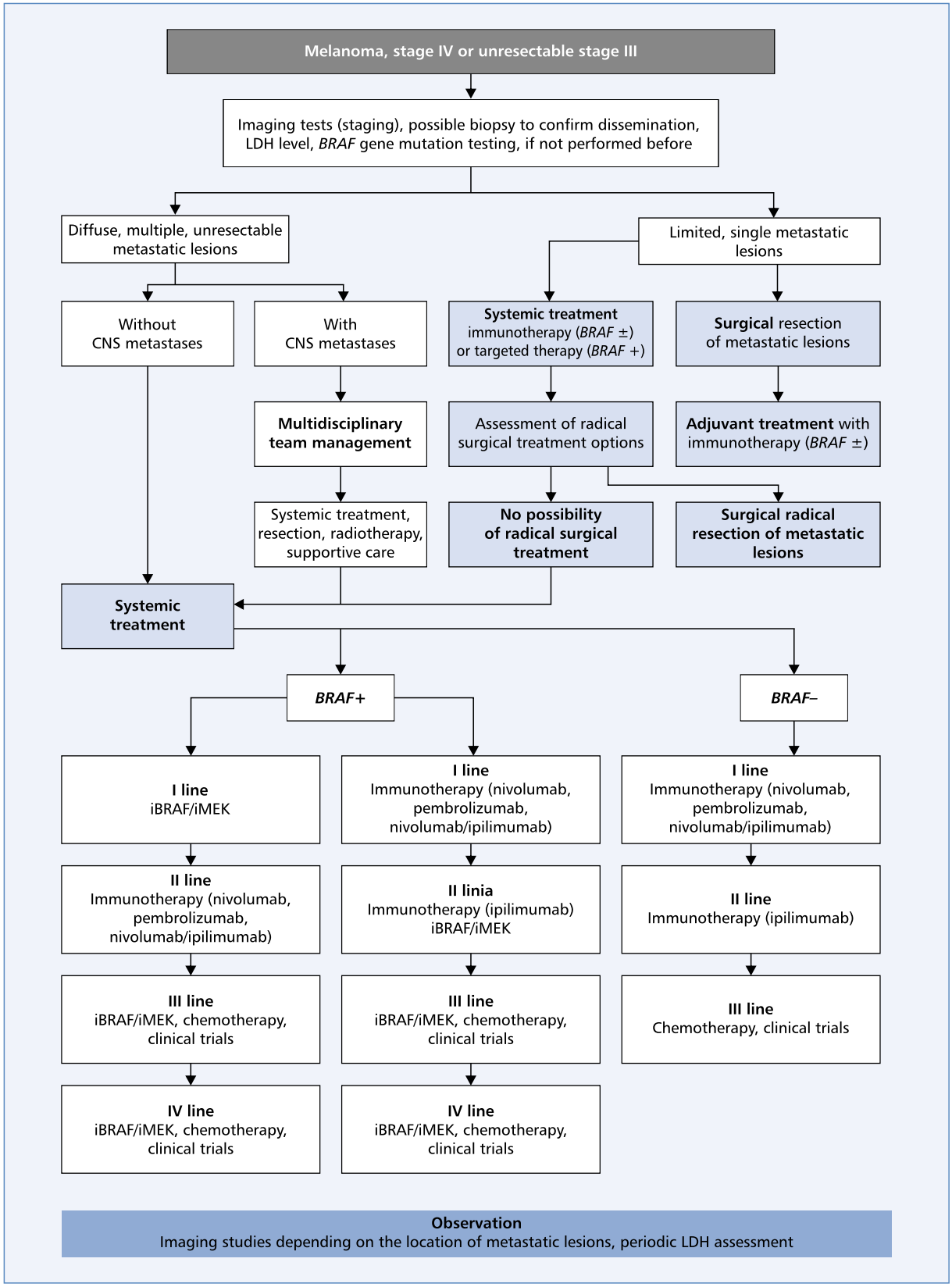

Figure 4. General algorythm of systemic treatment in patients with advanced stage IV or unresectable stage III melanomas; CNS — central nervous system; iBRAF — BRAF inhibitor; iMEK — MEK inhibitor; LDH — lactate dehydrogenase

Table 7. Treatment options in patients with relapse to the stage of unresectable disease after adjuvant treatment

Adjuvant treatment	First-line treatment of metastatic disease when disease relapse occurs during or < 6 months after completion of adjuvant therapy		First-line treatment of metastatic disease when disease relapse occurs > 6 months after completion of adjuvant therapy	
	BRAF gene mutations	*BRAF* WT (wild type)	*BRAF* gene mutations	*BRAF* WT (wild type)
Anti-PD-1	Anti-BRAF / MEK Ipilimumab + nivolumab Ipilimumab	Ipilimumab + nivolumab Ipilimumab	Anti-BRAF/MEK Ipilimumab + nivolumab Anti-PD-1 Ipilimumab	Ipilimumab + nivolumab Anti-PD-1 Ipilimumab
Anti-BRAF/MEK	Anti-PD-1 Ipilimumab + nivolumab		Ipilimumab + nivolumab Anti-PD-1 Anti-BRAF/MEK Ipilimumab	

of tumors by immunologically active cells in the early stage of therapy. To objectively assess the response to ipilimumab treatment, the use of immune response criteria is indicated [65–67].

The predictors of response to ipilimumab treatment have not been established yet. The recommended dose in monotherapy is 3 mg/kg body weight administered intravenously every 3 weeks, for a total of 4 doses (I, 1). The objective response rate after treatment with ipilimumab is low (approx. 10%), long-term benefits are achieved by a limited number of patients (20–25%), but they are associated with long-term survival (the longest follow-up is 10 years). The concerns connected with ipilimumab therapy are side effects related to autoimmune reactions (side effects in stages III–IV occur in about 20–25% of patients). The most common immune-related adverse events (irAE) are skin lesions, colitis (most often manifested by diarrhea), hepatotoxicity, and endocrine disorders (including hypopituitarism and thyroid gland insufficiency). In the case of significant symptoms worsening, glucocorticosteroids (prednisone at a dose of 1–2 mg/kg b.w./ /day or equivalent) should be administered immediately with further treatment in cooperation with a reference center. Appropriate management algorithms are available [66] and should be rigorously applied from the onset of the first symptoms suggesting immune-related toxicity. Treatment with ipilimumab should be carried out only in centers with highest levels of specialized care offering comprehensive diagnostic and therapeutic procedures. It is not justified to undertake the above-mentioned treatment in centers without full management capabilities. Ipilimumab monotherapy is not currently used in the first-line treatment of patients with advanced melanoma.

In the light of the current research results, ipilimumab monotherapy is not the basic type of immunotherapy in patients with advanced melanomas, as it gives worse outcomes than anti-PD-1 antibodies, with a worse safety profile. Treatment should be initiated with anti-PD-1 antibodies (nivolumab or pembrolizumab) in monotherapy or in combination with anti-CTLA-4 (I, 1).

Anti-PD-1 antibodies (nivolumab and pembrolizumab)

Currently, immunotherapy in cutaneous melanomas is mainly based on the use of PD-1 immune checkpoint blockade in monotherapy (nivolumab at a stable dose of 240 mg every 2 weeks or 480 mg every 4 weeks or pembrolizumab at a dose of 200 mg every 3 weeks or 400 mg every 6 weeks) (I, 1) [68–71] or in combination with anti-CTLA-4 antibodies (I, B) [72]. In clinical practice, these agents, in monotherapy or in combination with ipilimumab, showed long-term clinical benefits in some patients with advanced melanomas and significant response rates (up to 50%), with 1-year survival rates of 70–80%. The use of nivolumab or pembrolizumab is associated with a 2-year survival rate of 50–60% (median survival exceeds 2 years, the 3-year survival rate is approx. 45%), with acceptable toxicity (approx. 15% in stage III/IV, i.e. significantly less than for ipilimumab), although the most severe symptoms also relate to immune-related side effects. Studies have confirmed that pembrolizumab is more effective in terms of overall survival and progression-free survival compared to ipilimumab in first-line treatment and compared to chemotherapy after failure of previous therapy [68–70].

In a clinical study, treatment with the anti-PD-1 antibody, pembrolizumab, was used for up to 2 years. In the group of 104 patients who completed the 2-year treatment, 102 patients (98%) were still alive, and the 9-month progression-free survival rate was 91% (i.e. in the majority of patients disease control is maintained after discontinuation of active treatment). Based on the available literature data, discontinuation of immunotherapy with anti-PD1 antibody may now be considered in patients who maintain objective response (CR, PR)/ /clinical benefit (II, 2B) [73].

Anti-PD-1 antibodies with anti-CTLA-4 antibodies (nivolumab with ipilimumab)

The results of a clinical trial comparing the efficacy of nivolumab monotherapy, ipilimumab monotherapy, and a combination of both drugs showed that nivolumab was more effective than ipilimumab (median progression-free survival was 6.9 months *versus* 2.9 months, respectively). However, the most effective therapy (compared to ipilimumab) was a combination of these drugs (median progression-free survival 11.5 months) [73] (I, 1), although the study assumptions did not include a formal comparison of treatment results with the combination of nivolumab and ipilimumab and nivolumab monotherapy. The results of combined treatment with ipilimumab and nivolumab were better in patients with a *BRAF* gene mutation [74], and the 5-year overall survival rate in the combination arm was 52% (i.e. median OS exceeded 60 months) compared to 44% for nivolumab monotherapy [75]. Adverse events, grade III–IV according to the Common Terminology Criteria for Adverse Events (CTCAE), were observed significantly more often in the arm receiving combination therapy (56.5%), while in the arms with nivolumab and ipilimumab, it was 19% and 27%, respectively. Combined immunotherapy, rather than anti-PD1 monotherapy, may be the preferred option in patients with good performance status with poorer prognostic factors (including *BRAF* mutation, high LDH activity, mucosal melanomas [76–78] and asymptomatic CNS metastases) (II, 2A) [79, 80].

Molecularly targeted therapy

BRAF/MEK inhibitors

Mutations in the RAS/RAF/MEK/ERK pathway of MAP kinase (MAPK) are found in approx. 75% of skin melanomas. The dominant mechanism leading to RAS/RAF/MAPK pathway overactivity in skin melanoma is an activating mutation of the gene coding BRAF kinase, and somatic mutations of *BRAF* gene are actually detected in 50–70% of skin melanomas arising in places not exposed to long-term sunlight. The results of a pivotal phase III trial with vemurafenib in the first-line treatment in patients with *BRAF V600* mutations published in 2011 showed both responses to treatment in 48% of patients treated with BRAF inhibitor (iBRAF) *versus* 5% in patients receiving dacarbazine, and statistically significant improvement in progression-free survival (difference of approx. 5 months) and overall survival (difference approx. 3 months) [81].

Vemurafenib has been approved for the treatment of patients with advanced melanomas with a *BRAF* mutation (detection of this mutation is possible in Polish centers using a validated PCR test) (I, A). Although most patients eventually develop resistance to treatment (median progression-free survival is 6–7 months), the results of phase II–III studies showed median overall survival in patients with metastatic melanoma of 13–16 months, which is statistically significantly higher than previously observed in this group of patients. Vemurafenib is characterized by significant skin toxicity (hypersensitivity to UV radiation), hepatotoxicity typical for kinase inhibitors, and leads to the development of secondary neoplasms (skin cancer or keratoacanthoma in almost 20% of patients). Secondary skin cancers may develop as early as a few weeks after starting vemurafenib therapy. Their diagnosis is an indication for local treatment but does not require drug discontinuation. Adverse events often require a reduction of the vemurafenib dose. In 2012, the therapeutic efficacy of another BRAF inhibitor — dabrafenib (with efficacy comparable to vemurafenib, but with a different toxicity profile — including lower skin toxicity and a higher frequency of fever) was confirmed. Median PFS was 6.7 months for dabrafenib *vs.* 2.9 months for dacarbazine, and median overall survival reported in 2013 for dabrafenib was 18.2 months (I, 1) [82]. A phase III clinical trial also confirmed the efficacy of the MEK inhibitor (iMEK) — trametinib — in the treatment of patients with metastatic melanomas with *BRAF* gene mutations (I, 2B) [83].

The efficacy of MEK inhibitors was also observed in patients with *NRAS* mutations (II, 2B) [84].

The results of recent studies (COMBI-d, COMBI-v, coBRIM, and COLUMBUS) have shown that in patients with metastatic melanomas with *BRAF* gene mutations, the use of a combination of BRAF and MEK inhibitors (dabrafenib with trametinib, vemurafenib with cobimetinib, or encorafenib with binimetinib) is more beneficial than monotherapy with BRAF inhibitor allone, improving the quality of life without increasing toxicity and with improving the quality of life (I, 1) [85–91]. Median overall survival due to treatment with these agents is extended to approx. 23–33 months, with median progression-free survival of approx. 12–14 months [91–93]. The best overall survival is obtained in patients with normal LDH activity and metastases in fewer than 3 organs.

All drug combinations are currently available in Poland in the first or subsequent treatment lines for patients with advanced melanomas with confirmed presence of *BRAF V600* mutation and reimbursed within the B.59 drug program. These drugs also have a beneficial effect in patients with stable and/or asymptomatic brain metastases.

A new option of targeted therapy is reintroduction of combination therapy with BRAF and MEK inhibitors after their early discontinuation due to disease progression. A phase II study showed that 8 out of 25 patients (32%) achieved partial remission of the disease after reintroduction of treatment with dabrafenib and trametinib, and further 40% of patients achieved stabilization with the median progression-free survival of 4.9 months [94]. During the 2017 ASCO Annual Meet-

ing, an analysis of 116 patients with advanced melanoma receiving BRAF inhibitor and BRAF ± MEK inhibitor therapy after a treatment interruption (related to the indication for next line treatment after progression during previous therapy) was presented. The median duration of this therapy used for the first time was 9.4 months and 7.7 months after rechallenge of targeted therapy. The response rate after rechallenge of treatment with BRAF ± MEK inhibitors was 43%: complete responses — 3%, partial responses — 39%, and disease stabilization — 24% and disease progression — 30%, no data — 4%. Median overall survival from rechallenge was 9.8 months (III, 2A) [95, 96].

KIT kinase inhibitors

In rare cases of patients with melanomas with *KIT* mutations, the activity of KIT kinase inhibitors has been observed; KIT kinase inhibitors are not reimbursed for this indication (II, B) [97].

Sequencing of systemic therapy

There is no definitive data on the optimal sequence of immunotherapy and targeted therapy in patients with *BRAF*-mutant melanomas. It should be noted that the activity of BRAF inhibitors is preserved after prior immunotherapy, and the effectiveness of immunotherapy (anti-PD-1) occurs after prior treatment with BRAF inhibitors (Fig. 3) [98]. The recent trials indicate that long-term effects in *BRAF*-mutated melanoma patients is achieved when first-line line therapy is a combination of nivolumab and ipilimumab. There is also a lack of significant data regarding the preferred systemic treatment in the case of inoperable relapse or metastatic spread after previous adjuvant therapy (Tab. 4 summarizes the ESMO consensus recommendations for this clinical situation) (IV, 2B) [99]. Since BRAF inhibitors (+ MEK inhibitors) treatment in patients with advanced *BRAF*-mutant melanomas result in rapid tumor response and control in most patients, with limited responce duration associated with activation of resistance mechanisms, these agents should be considered as the treatment of choice in patients who are symptomatic and have significant disease dynamics and/or large tumor burden.

Combination therapy

In 2020, the results of the phase III IMspire150 study were published, in which patients with advanced melanoma (unresectable stage IIIC/IV) with *BRAF* gene mutations were randomly assigned to first-line treatment with triple combination of atezolizumab (anti-PD-L1 immunotherapy), vemurafenib, and cobimetinib or placebo, vemurafenib, and cobimetinib (the control group). The study found a clinically and statistically significant improvement in investigator-assessed PFS in the atezolizumab group compared to placebo (15.1 *vs*. 10.6 months; HR 0.78; 95% CI 0.63–0.97; p= 0.0249) [100]. Response duration was also significantly longer in the atezolizumab arm (21 months) compared to the control arm (12.6 months) (II, 2B). The triple combination seems to be an interesting option, although the long-term results may be comparable to the combination of ipilimumab with nivolumab. Currently, its role is not defined, and it is approved only in the United States.

Inhibitor LAG-3 (relatlimab) in combination with nivolumab improved significantly progression-free survival as compared to anti-PD-1 monotherapy in patients with previously untreated metastatic or unresectable melanoma [II, 2A] [101] — this combination is approved but not reimbursed in Poland.

Rehabilitation

Patients treated for melanoma after axillary or inguinal lymph nodes resection may experience ipsilateral limb lymphoedema. Edema is less likely after the sentinel lymph node biopsy.

Lymphoedema is an excessive accumulation of protein-rich fluid in the intercellular spaces. This leads to chronic inflammation, fibrosis and periarticular changes, and emotional changes due to chronic, progressive dysfunction (Tab. 9). According to the published data, the rate of development of lower limb edema after biopsy of inguinal sentinel lymph nodes ranges from 7.6 to 35.1%, and after lymphadenectomy from 48.8 to 82.5%. The upper limb edema rate after axillary lymphadenectomy ranges from 4.4 to 14.6% [102].

Physiotherapy of patients with post-treatment lymphedema [103]

Patients with secondary edema have a reduced quality of life (EORTC QLQ C30 studies). In the group of patients after lymph nodes resection, prevention of edema should be applied: patients with a high probability of edema should be provided with compression sleeves of the 1st degree of compression (ipsilateral upper limb) and compression hosiery of the 1st–2nd degree of compression to prevent swelling of the lower limb (they should be used for at least 6 months after surgery).

Physical examination of lymphoedema consists of line measurements, water displacement/perometer tests, and palpation to determine swelling degree and consistency. The fold test should be applied, and the Stemmer sign should be considered.

If secondary edema occurs, patients should be referred to specialized centers conducting the rehabilitation of patients with secondary lymphoedema. Such procedures include comprehensive decongestant therapy (lymphatic drainage with compression, kinesitherapy, mechanical pneumatic massage, and other procedures dedicated to this group of patients).

Table 8. Recommended follow-up evaluations in patients with skin melanoma

Melanoma stage	Test	Frequency
Early melanomas after excision of primary lesion without metastases in lymph nodes (stages IA–IIA)	Medical history and physical examination, including full-body skin surface, area of scar after melanoma excision and regional lymph nodes Chest X-ray — optionally US of regional lymph nodes when sentinel lymph node biopsy not done in melanomas ≥ pT1b No indications for routinely performed imaging and laboratory tests Additional examinations (CT with contrast or PET-CT of the chest, abdominal cavity, pelvis ± neck and MRI of CNS or other) always in case of clinical symptoms Patient education including risk factors and self-monitoring (assessment of the skin and lymph nodes)	Every 6–12 months during first 5 years, then yearly if clinically indicated (control is possible outside specialized center)
Locally advanced melanomas after excision of primary lesion without metastases in lymph nodes (stages IIB–IIC)	Medical history and physical examination, including full-body skin surface, area of scar after melanoma excision and regional lymph nodes Chest X-ray, abdominal US — optionally US of regional lymph nodes when sentinel lymph node biopsy not done in melanomas ≥ pT1b Imaging tests (CT with contrast or PET-CT of the chest, abdominal cavity, pelvis and neck and MRI of CNS) should be considered every 3–12 months for the first 2 years, then every 6–12 months for the next 3 years. There are no indications for routine imaging after 3–5 years. No indications for routinely laboratory tests Additional examinations (CT with contrast or PET-CT of the chest, abdominal cavity, pelvis ± neck and MRI of CNS or others) always in case of clinical symptoms. In patients with melanomas IIB–IIC CT could be performed every 6–12 months, and brain MRI optionally yearly during first 2–3 years Patient education including risk factors and self-monitoring (assessment of the skin and lymph nodes)	Every 3–6 months during first 2–3 years, then every 6–12 months until 5 years, and then yearly after 5 years if clinically indicated
After excision of metastases in local lymph nodes or local recurrence/satellite lesion/in-transit metastasis (stages IIIA–IIID) or follow-up after sentinel lymph node metastasis without complementary lymphadenectomy	Medical history and physical examination, including full-body skin surface, area of scar after melanoma excision and regional lymph nodes Chest X-ray — optionally Nodal basin US for regional lymph node assessment every 4–6 months in the case of positive sentinel lymph node without lymphadenectomy Imaging tests (CT with contrast or PET-CT of the chest, abdominal cavity, pelvis ± neck and MRI of CNS) should be considered every 3–12 months for the first 2 years, then every 6–12 months for the next 3 years, especially in stage IIIC/IIID. There are no indications for routine imaging after 3–5 years No indications for routinely laboratory tests Additional examinations (CT with contrast or PET-CT of the chest, abdominal cavity, pelvis ± neck and MRI of CNS or others) always in case of clinical symptoms. In patients with melanomas IIB–IIC CT could be performed every 6–12 months, and brain MRI optionally yearly during first 2–3 years Patient education including risk factors and self-monitoring (assessment of the skin and lymph nodes)	Every 3–4 months during first 2 years, every 3–6 months during subsequent 3 years, and yearly after 5 years if clinically indicated
After treatment of distant metastases (stage IV)	Assessment of metastatic lesions in imaging tests (CT with contrast or PET-CT of the chest, abdominal cavity, pelvis ± neck and MRI of CNS or others) depending on location. Lactate dehydrogenase serum level	Follow-up visit schedule individualized for every patient

CNS — central nervous system; CT — computed tomography; LDH — lactate dehydrogenase; MRI — magnetic resonance imaging; US — ultrasound examination

Table 9. Stages of lymphoedema

Stage	Clinical manifestations	Conservative therapy
I (implicit)	Lymph transport volume decreased Swelling not visible Subjective, negative patient's feelings	Limb elevation Self-massage Prophylactically compression sleeve or hosiery of the 1st degree of compression
II	Accumulation of protein-rich fluid Visible, soft swelling	Limb elevation Self-massage Physical activity Prophylactically compression sleeve or hosiery of the 1st degree of compression
III	Accumulation of protein-rich fluid Hard swelling The onset of fibrosis	Comprehensive decongestion therapy Compression products (compression sleeve or hosiery)
IV	Accumulation of protein-rich fluid Hard swelling Fibrosis Skin changes (mycoses, eczema)	Comprehensive decongestion therapy Compression products (compression sleeve or hosiery)

After therapy is completed, it is recommended to put on a sleeve or hosiery to support the effects of anti-edema therapy. Compression materials supporting the effects of anti-edema therapy should be tailored to the degree of edema (size, volume of the affected limb). Currently, custom-made sleeves and hosieries are partially reimbursed by the National Health Fund (NFZ) [104].

Study results show that it is very important to inform patients treated for melanoma with sentinel lymph node biopsy or lymphadenectomy about the possibility of secondary lymphoedema and preventive measures. One of the elements of prophylaxis is also physical activity [105, 106].

Follow-up after treatment

The frequency and type of examinations, as well as the duration of the observation period, should depend on the individual risk of disease recurrence (which depends on the initial disease stage) (II, 2A), but one should remember about the possibility of relapse after more than 10 years from the initial treatment [107, 108] (Tab. 5).

The risk of recurrence is highest in the first 3 years after treatment; therefore, recommended follow-up schedules include intensified control during this period, mainly to detect possible loco-regional recurrence, which potentially gives a chance of radical surgical treatment. The basis of post-treatment follow-up is the evaluation of scars following primary excision and lymphadenectomy. Particular care must be taken in assessing the regional lymph nodes (possible *in-transit* spreading). For the assessment of regional lymph nodes, an ultrasound examination is also recommended in addition to the physical examination. As a large proportion of loco-regional recurrences can be detected by the patient (even > 60%), patient awareness should be raised about the importance of self-examination of the area after resected primary melanoma and regional lymphatic drainage. There are premises that in patients with early-stage melanoma, less intensive control regimens do not adversely affect survival.

Imaging tests are not justified during observation of asymptomatic patients in stages IA–IIA; they can be considered for the first 2–3 years (e.g. CT scan) in asymptomatic patients with stages IIB–IIIC (taking into account the recent emergence of new effective drugs for the treatment of disseminated melanomas (IV, 2B), as earlier data showed a minimal gain of up to 2 months in relation to the expected survival benefit from intensive schedules of imaging studies). In turn, in patients with clinical symptoms suggesting the presence of distant metastases (liver enzyme elevation, bone pain, neurological symptoms, cough, and weakness), detailed imaging diagnostics, including CT, MRI, PET-CT, and bone scintigraphy, should be performed.

During follow-up examinations, it is necessary to examine full-body skin (not only the area where cancer previously developed), due to the statistically greater chance of developing a second independent melanoma lesion or other skin cancer.

Additional information for patients is available, among others, on the websites of scientific societies (e.g. www.akademiaczerniaka.pl).

Conclusions

A biopsy that excludes atypical and suspicious pigmented lesions, which may be early melanomas, is of fundamental importance in the diagnosis and determination of

the most important prognostic factors (microstaging I). Early diagnosis and resection of melanoma not only improves the prognosis but also gives a chance of recovery in nearly 90% of patients. Typically, pigmented lesions of up to 2 cm in the transverse axis can be removed on an outpatient basis as part of a resection that meets the definition of excisional biopsy. The next steps of the procedure include qualification of patients for radical resection of the scar after excisional biopsy with appropriate margins of 0.5–2 cm depending on Breslow thickness and the performance of a sentinel lymph node biopsy (stage ≥ pT1b). In the case of clinically detected metastases in regional lymph nodes, radical lymphadenectomy is the treatment of choice. It is recommended to qualify patients with high-risk skin melanomas to systemic adjuvant therapy (nivolumab, pembrolizumab, dabrafenib with trametinib). The algorithms of diagnostic and therapeutic management in patients with skin melanomas are presented in Figures 2–4.

The presence of distant metastases is still associated with a poor prognosis. In patients with metastatic disease, enrollment in a clinical trial is the most appropriate approach. In patients with generalized disease or associated with a high risk of disease recurrence (stage III), it is recommended to test *BRAF* gene status.

Long-term survival is concerning in stage IV patients who underwent resection of single metastatic lesions. In systemic treatment — primarily in the first line — in patients with the presence of *BRAF V600* mutations, BRAF inhibitor (in combination with MEK inhibitor) is used and, regardless of *BRAF* mutation status, immunotherapy with anti-PD-1 antibodies (nivolumab or pembrolizumab), ipilimumab (anti-CTLA4 antibody alone or in combination with anti-PD-1). The optimal treatment sequence (especially in the presence of a *BRAF* gene mutation) is currently not defined. The use of combined therapy with BRAF and MEK inhibitors is associated with a high response rate (approx. 70%) and a rapid relief of disease symptoms, while treatment with anti-PD-1 antibodies results in lower response rates, but they are mostly long-lasting and persist also after treatment discontinuation.

Part II
Ocular melanoma

Uveal melanoma

Epidemiology and etiology

Uveal melanoma is the most common primary intraocular malignant neoplasm in adults. It is significantly different from conjunctival, mucous, and skin melanoma [109]. According to the 2018 National Cancer Registry (NCR) data, ocular neoplasms (C69) account for 0.3% of all neoplastic diseases in Poland (523 cases), and most of them are uveal melanomas. Mortality from this malignant tumor was 0.1% (121 deaths) [110]. The prevalence varies by ethnic group and latitude. The incidence is highest among Caucasians (98% of all patients) and at higher latitudes. In Mediterranean countries, 2 new cases per 1 million inhabitants per year are reported, while in Scandinavian countries it is 8–11/1 million inhabitants. In the United States of America, on average, 4.3 new cases occur per 1 million inhabitants per year [111–114].

Children rarely suffer from this type of cancer, and their prognosis is significantly better (5-year and 10-year survival rates are 97% and 92%, respectively) [115, 116].

Melanoma develops from the melanocytes of the uveal layer, affecting particular areas of the uveal layer with different frequencies. About 4–6% of ocular melanomas are found in the iris, 6–9% in the ciliary body, and most often in the choroid (85–90%) [117–119].

Staging and prognostic factors

The prognosis of uveal melanoma depends on many factors. One of them is the size of the primary tumor (the largest diameter of the base and height). Larger tumors are associated with worse survival. Increasing the tumor height by 1 mm increases the risk of metastasis by 5% within 10 years. Based on the assessment of thickness (height), tumors were divided into 3 groups: the small (0–3 mm), medium (medium; 3.1–8.0 mm), and large (> 8 mm) groups. Five-, 10- and 20-year mortality in particular groups was 6%, 12%, and 20%, respectively, then 14%, 26%, and 37%, and in the last group — 35%, 49%, and 67% [120, 121]. Another factor adversely affecting the prognosis is the involvement of the ciliary body. In these cases, 33% of patients metastasize during the 10-year follow-up, as opposed to 7% when the neoplasm covers the iris or up to 25% for the choroid [119, 120]. Other factors that worsen the prognosis and are associated with a greater tendency to metastasize are the following histopathological features: epithelial type melanoma, deep infiltration of eyeball wall (sclera), presence of extraocular infiltrates, high mitotic index, optic nerve infiltration, own vascularization of the tumor with a tendency to form arches branches, closed loops and vascular networks, as well as inflammatory tumor infiltration (especially by T lymphocytes and macrophages) [119, 122–124].

Genetic disorders such as monosomy 3, multiple copies of 1q, 6p, and 8q, loss of 1p, 6q, and 8p, and mutations in the *BAP1*, *GNAQ,* and *GNA11* genes are associated with a high risk of metastases. In contrast, mutations in the *EIF1AX* gene are associated with a good prognosis [119, 125].

Local control after the treatment of uveal melanoma is very high (86–98%) and is achieved through using various conservative treatment methods, such as brachytherapy, proton therapy, transpupillary thermotherapy (TTT), tumor endo- or exoresection, and their different combinations. In very large tumors, i.e. with a base diameter greater than 20 mm or a height greater than 12 mm, and if the tumor extensively affects the optic nerve, the best treatment is still enucleation (see below) [126]. A big problem in this disease is still high mortality of approx. 50% due to generalized dissemination, with no effective treatment in such cases. In over 90% of cases, the metastases are located in the liver despite good effects of local treatment. This is due to the tendency of uveal melanoma to metastasize in the early stages of its development (formation of micrometastases) and the presence of cancer cells in the vascular bed prior to treatment [119, 127].

The AJCC TNM classification, developed by the American Joint Committee on Cancer, is used for staging and prognosis assessment of uveal melanoma. It takes into account the size of the largest tumor base, its thickness (height), involvement of the ciliary body, presence, and size of extraocular infiltration and presence of metastases [128] (Tab. 10–14). Involvement of the surrounding lymph nodes in uveal melanoma is extremely rare. To assess the risk of metastasis, the above-mentioned genetic testing should also be considered, including first of all, monosomy 3 and the *BAP1* gene mutation [119] (III, 2B).

Signs and symptoms

About one-third of patients with uveal melanoma are asymptomatic, and if any symptoms occur, they are uncharacteristic. Patients most often report decreased visual acuity and visual field disturbances. Pain may also occur due to elevated intraocular pressure, as well as a veil in front of the eye or image distortion [129].

Diagnostic tests

1. Ophthalmological examination of the anterior segment of the eyeball in a slit lamp (III, 2A).

Table 10. Primary tumor — T feature

All uveal melanomas	
TX	Primary tumor cannot be assessed
T0	No primary tumor
Iris	
T1	Tumor limited to the iris
T1a	Tumor limited to the iris, not more than 3 clock hours in size
T1b	Tumor limited to the iris, extending more than 3 clock hours
T1c	Tumor limited to the iris with secondary glaucoma
T2	Tumor of the iris involving the ciliary body and/or the choroid
T2a	Tumor of the iris involving the ciliary body and/or the choroid with secondary glaucoma
T3	Tumor of the iris involving the ciliary body and/or the choroid with scleral infiltration
T3a	Tumor of the iris involving the ciliary body and/or the choroid with scleral infiltration and secondary glaucoma
T4	Melanoma with extraocular infiltration
T4a	Extraocular infiltration of iris melanoma with greatest diameter ≤ 5 mm
T4b	Extraocular infiltration of iris melanoma with greatest diameter > 5 mm
Ciliary body and choroid	
T1	Tumor of the first size category
T1a	Tumor of the first size category without involvement of the ciliary body and retrobulbar infiltration
T1b	Tumor of the first size category with involvement of the ciliary body
T1c	Tumor of the first size category without involvement of the ciliary body, but with a retrobulbar infiltrate with the largest diameter ≤ 5 mm
T1d	Tumor of the first size category with involvement of the ciliary body and with the largest retrobulbar infiltrate of the largest diameter ≤ 5 mm
T2	Tumor of the second size category
T2a	Tumor of the second size category without involvement of the ciliary body and retrobulbar infiltration
T2b	Tumor of the second size category with involvement of the ciliary body
T2c	Tumor of the second size category without involvement of the ciliary body, but with a retrobulbar infiltrate with the largest diameter ≤ 5 mm
T2d	Tumor of the second size category with involvement of the ciliary body and with retrobulbar infiltration with the largest diameter ≤ 5 mm
T3	Tumor of the third size category
T3a	Tumor of the third size category without involvement of the ciliary body and retrobulbar infiltration
T3b	Tumor of the third size category with involvement of the ciliary body
T3c	Tumor of the third size category without involvement of the ciliary body, but with a retrobulbar infiltrate with the largest diameter ≤ 5 mm
T3d	Tumor of the third size category with involvement of the ciliary body and with retrobulbar infiltration with the largest diameter ≤ 5 mm
T4	Tumor of the fourth size category
T4a	Tumor of the fourth size category without involvement of the ciliary body and retrobulbar infiltration
T4b	Tumor of the fourth size category with involvement of the ciliary body
T4c	Tumor of the fourth size category without involvement of the ciliary body, but with a retrobulbar infiltrate with the largest diameter ≤ 5 mm
T4d	Tumor of the fourth size category with involvement of the ciliary body and with retrobulbar infiltrate with the largest diameter ≤ 5 mm
T4e	Tumor of any category with retrobulbar infiltration with the largest diameter > 5 mm

[a]In order to determine the T feature in ciliary body and choroidal melanoma, it is necessary to first classify the tumor into the appropriate size category based on height and the largest tumor base diameter (Tab. 11)

Table 11. Regional lymph nodes — N feature

Nx	Regional lymph nodes cannot be assessed*
N0	No metastases in regional lymph nodes
N1	Metastases in regional lymph nodes or separate orbital neoplastic deposits
N1a	Metastases in one or more regional lymph nodes
N1b	Separate orbital neoplastic deposits without continuity with the eyeball, no metastases in regional lymph nodes

*Regional lymph nodes include preauricular, submandibular, and cervical lymph nodes

Table 12. Distant metastases — M feature

M0	No distant metastases
M1	Distant metastases present
M1a	Diameter of largest distant metastasis ≤ 3 cm
M1b	Diameter of the largest metastasis 3.1–8.0 cm
M1c	Diameter of the largest metastasis > 8 cm

2. Eye fundus examination after pupil dilation (preferably indirect ophthalmoscopy) (III, 2A).
3. Ultrasound examination (III, 2A):
   a. ultrabiomicroscopy — ultrasound examination of the anterior segment of the eyeball, ciliary body, and the front part of the choroid;
   b. ultrasonography of the posterior segment of the eyeball (detection of a mushroom-shaped tumor is a typical feature of uveal melanoma).
4. Optical coherence tomography (OCT) (III, 2A).
5. Taking a photo of the observed lesion to determine any progression (III, 2A).
6. Gonioscopy when it is suspected that the lesion is occupying or reaching filtration angle (III, 2A).
7. Diaphanoscopy or transillumination (reveal tumor base) (III, 2A).
8. Additional examinations (performed in case of diagnostic doubts) (III, 2B):
   a. fluorescein angiography (FA),
   b. indocyanine green angiography (ICGA),
   c. computed tomography of orbits,

Table 13. Melanoma staging

Stage	Feature T	Feature N	Feature M
I	T1a	N0	M0
IIA	T1b–d	N0	M0
	T2a	N0	M0
IIB	T2b	N0	M0
	T3a	N0	M0
IIIA	T2c–d	N0	M0
	T3b–c	N0	M0
	T4a	N0	M0
IIIB	T3d	N0	M0
	T4b–c	N0	M0
IIIC	T4d–e	N0	M0
IV	Any T	N1	M0
	Any T	Any N	Any M1 a–c

Prefixes: y — preoperative radiotherapy or chemotherapy; r — tumor recurrence

Table 14. Histological grading — G feature

GX	Histological grade cannot be assessed
G1	Spindle cell melanoma (> 90% of spindle cells)
G2	Mixed cell melanoma (> 10% epithelial cells and < 90% spindle cells)
G3	Epithelial cell melanoma (> 90% of epithelial cells)

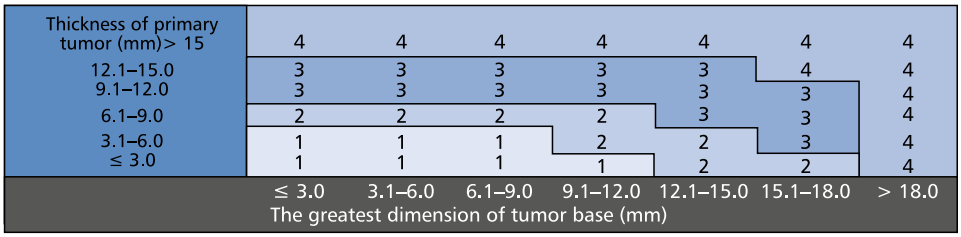

Figure 5. Classification of ciliary body and uveal melanoma based on thickness and size of the primary tumor (mm)

d. magnetic resonance imaging of orbits, autofluorescence [130].

9. Tumor biopsy remains controversial due to the increased risk of dissemination and the high rate of false-negative results [131] (III, 2A) [132] (NCCN Guidelines. Uveal Melanoma. Version 3.2020).

Differential diagnostics

Uveal melanoma is most often differentiated from metastatic tumors of a different location and with pigmented nevi. It is very important to distinguish the atypical, pigmented nevus from small melanoma (TFSOM rule developed by Shields et al.) [133] (III, A).

Less frequently, the differential diagnosis includes choroidal hemangioma (limited or diffuse), intraocular lymphoma, retinal hemangioma, osteoblastoma, retinochoroidal calcification, astrocytoma, and age-related macular degeneration (AMD), especially the wet (exudative) form [130, 134].

Remarks

The greatest tumor diameter and thickness (height) are used to define the size category (Tab. 10, Fig. 5). The determination of pT is required for ciliary and choroidal melanomas but is only feasible if the primary treatment was enucleation of the eyeball. In these situations, a proper technique is essential to visualize the greatest tumor base diameter and thickness (height) in the removed eyeballs. For this purpose, the eyeball should be X-rayed with a strong light source to map the shadow of the tumor on the sclera and determine its position in relation to the optic nerve.

The eyeball should be cut so that the cross-sectional plane contains the greatest tumor base diameter, rests on the shadow, and passes through the center of the disc, as well as the optic nerve.

In the past, in the clinical assessment of tumor dimensions, the greatest base diameter was expressed in multiples of the optic disc diameter (dd) (averagely 1 DD = 1.5 mm), and tumor thickness (height) in diopters (averagely 3 diopters = 1 mm). Currently, the standard is to determine the size of intraocular tumor parameters in millimeters based on measurements performed in an ultrasound examination (determination of T feature). It should be noted that most patients with uveal melanoma are treated conservatively, so ultrasonography remains the only method to assess tumor size.

Treatment

Local treatments for uveal melanoma can be divided into two main types.

Conservative

Conservative treatment to preserve the eyeball and even, in some cases, useful visual acuity. This type of therapy includes:

1. Radiotherapy in the form of (III, 2A):
   - **a. Brachytherapy** (most frequently used) with the use of various radioactive elements, which allows for very good local tumor control of 95–98% [135, 136]. The isotopes of ruthenium-106 (Ru-106) and iodine-125 (I-125) are commonly used. Palladium (Pd-103) and iridium (Ir-192) are used much less frequently due to the short half-life and very high costs of therapy. Ru-106 is effective in treating tumors up to 5 mm in height, or up to 6 mm in height, but in combination with transpupillary thermotherapy (TTT). I-125 is used to treat tumors of thickness ranging from 5 mm to 10–12 mm. An important factor determining the use of applicators is also tumor base, which should not exceed the diameter of the applicator and may not exceed 18 mm, which allows for a safe margin [137]. The dose at the tumor top should not be less than 70 Gy, and for I-125 preferably around 82.5 Gy [137–141].
   - **b. Proton radiotherapy** — a positive local result is obtained in 95–98% of cases. The therapy uses a collimated beam of protons or helium nuclei. Irradiation is performed for 4 consecutive days with a total dose of 60 Gy at the tumor top (4 × 15 Gy) [142].
   - **c. Stereotactic radiotherapy**

2. Local, sparing surgical treatment (III, 2A)
   a. Local resection:
— Exoresection — is used to treat lesions located in the iris, ciliary body, or the anterior choroid. The tumor is removed under the scleral flap in combination with brachytherapy.
— Endoresection — can be performed after prior radiotherapy. The tumor is removed during *pars plana* vitrectomy (PPV) [143–145].
3. Laser treatment
   a. Transpupillary thermotherapy (TTT) is intended for the treatment of small melanomas. Most often used with brachytherapy, especially in the parathyroid tumor localization, it is the so-called sandwich therapy (III, 2B).
   b. Photodynamic therapy — experimental and controversial therapy with the use of a photosensitizing dye (verteporfin) for the treatment of amelanotic, small melanomas [146, 147] (IV, C).

Radical surgery

1. **Enucleation**, i.e. removal of the eyeball. Recommended when the tumor thickness and base diameter are over 12 mm and over 20 mm, respectively, and when the tumor infiltrates the optic nerve or there is secondary glaucoma [126] (III, 2A).
   It is recommended to implant an orbital implant tight after after enucleation provided that there are no signs of extraocular infiltration, and prosthesis of the orbit is performed up to 14 days after the surgery.
2. **Exenteration**, i.e. evisceration of the orbit is indicated in the case of massive extraocular infiltration.

Treatment in the generalized stage

Treatment of generalized uveal melanoma allows extending the survival by a few months, especially if it is possible to use local treatment methods for liver metastases [148]. Surgical resection (if single lesions are present, which is rare), chemoembolization/radioembolization or thermoablation of liver metastases, and systemic treatment are used [119, 149] (III, A). In clinical trials, attempts are made to use therapies affecting the PKC-MAPK pathway, modifying epigenetic mechanisms (e.g. Vorinostat) or immune checkpoints inhibitors (small effects were observed in phase II studies mainly with the combination of nivolumab and ipilimumab) [150, 151]. These studies have so far failed to show positive results [119, 152], except for the data on the use of tebentafusp (IMCgp100), a novel bispecific molecule targeting T cells in the presence of HLA-002, which was compared to historical data (phase II study [153] — median OS 16.8 months) and an active comparator (phase III study — 1-year OS rate 73% *vs.* 58%, HR 0.51) — this drug is registered in the European Union, but not reimbursed in Poland [154].

Follow-up and treatment of local complications

After treatment of uveal melanoma, the patient should undergo ophthalmological examination every 3–6 months in the first 2 years, and every 6–12 months in the following years. The examination should aim to detect a potential local recurrence or complications after therapy. After conservative treatment, it should include at least visual acuity, intraocular pressure measurement, slit-lamp anterior segment examination, and eye fundus examination after pupil dilation, US, photography, and OCT. In turn, after the enucleation, the orbit should be examined (after removal of the epiprosthesis, the orbit should be inspected and palpated), and control MRI examinations of the orbits should be performed every 6–12 months [155, 156] (III, A).

As a result of the applied conservative treatment, there is a risk of complications in the form of cataracts, secondary glaucoma, iris neovascularization, retinopathy (with maculopathy), and neuropathy. All these complications should be treated, but what is even more important, they should be prevented. The best method of treating retinopathy, maculopathy, and post-radiation neuropathy, as well as iris neovascularization, are intravitreal injections or injections into the anterior chamber of anti-VEGF agents or steroids. In the case of anti-VEGF agents, it is recommended to initially administer 3 injections with an interval of 1–2 months (depending on the type of drug), and then depending on the clinical picture [157, 158] (III, A).

After ophthalmic treatment, the patient should remain under control to monitor and treat any metastases. For this purpose, it is recommended to perform magnetic resonance imaging, possibly computed tomography or ultrasound of the abdominal cavity every 3–12 months, and liver tests every 3–6 months (monitoring towards liver metastases). Chest X-ray is recommended every 12 months [156, 159] (III, A).

Conjunctival melanoma

Conjunctival melanoma is a very rare neoplasm, which accounts for 0.25% of all melanomas and 5% of ocular melanomas. In recent years, a significant increase in the incidence of this type of cancer has been observed [160, 161]. Molecular aspects of the development of conjunctival melanoma include mutations in *BRAF* and *NRAS* genes, which are completely different from those reported in uveal melanoma [1] (III, 2A).

The vast majority, i.e. 74%, of melanomas, develop upon primary acquired melanosis (PAM), 7% from a nevus, and 19% *de novo* [160, 162] (III, 2A).

Local recurrence takes place in 30–50% of patients within 5 years [163].

Metastasis occurs in approximately 20–30% of patients over 10-year follow-up [160]. Factors associated with a worse prognosis include tumor localization outside the conjunctiva, multinodular type of growth, rapid growth, tumor thickness > 2 mm, recurrence, incomplete resection, and failure to apply adjuvant therapy after resection [160, 164] (III, 2A).

The mainstay of treatment is surgical tumor resection after prior closure of nutrient vessels, with a macroscopically preserved margin of healthy tissue, the size of which remains undefined [160, 164] (III, 2A). Some recommend the use of cryotherapy in sites after resection and swabs with absolute alcohol [160, 165] (IIIB). In very advanced cases, enucleation and exenteration are considered [160, 166, 167] (III, 2A).

The adjuvant treatment includes:

1. Local chemotherapy:
   a. Mitomycin C, which is administered to the conjunctival sac two weeks after surgery [160, 168–173] — not reimbursed use, with very limited clinical data (IV, 2B)
   b. Interferon alfa-2b [160, 174, 175] (IV, 2B)
2. Radiotherapy:
   a. EBRT
   b. Local brachytherapy.

Sentinel lymph node biopsy should be considered, however, bearing in mind that distant metastases occur in 50% of cases, without the presence of neoplastic cells in the surrounding lymph nodes [160, 176, 177] (III, 2B).

Therapeutical options in patients with metastatic conjunctival melanoma include the same treatments as for advanced cutaneous melanoma [160] (III, 2A).

After the treatment of conjunctival melanoma, the patient should remain under constant oncological and ophthalmological monitoring (photographic documentation of the local condition is important every time; it is recommended to check the conjunctiva after turning the eyelids outwards).

Conflict of interest

P. Rutkowski received fees for lectures and participation in Advisory Boards from Novartis, BMS, MSD, Pierre Fabre, Merck, Sanofi, Amgen, Blueprint Medicines. E. Kalinka and A. Czarnecka received fees for lectures and clinical trials from BMS, MSD, Roche. Andrzej Kawecki received fees from the following companies: BMS: fees for lectures and participation in Advisory Board, conducting clinical trials; MSD: fees for lecture and participation in Advisory Board; Merck: fees for lecture and participation in Advisory Board, Sanofi: fees for participation in Advisory Board. M. Ziobro received fees for lectures and participation in Advisory Boards from Novartis, BMS, MSD, Pierre Fabre, Merck, Amgen, Roche, Pfizer. B. Cybulska-Stopa received fees for lectures and participation in Advisory Boards from Novartis, BMS, MSD, Pierre Fabre.

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