Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 102 (2018) 30-46 EISSN 2392-2192

Current clinical management of malignant melanoma – diagnosis process and innovative therapies

Stanisław Kwiatkowski[1,*], Dawid Przystupski[1], Krzysztof Kotowski[1], Karolina Kolasińska[1], Jolanta Saczko[2,3], Julita Kulbacka[2,3]

[1]Faculty of Medicine, Wroclaw Medical University,
5, J. Mikulicza-Radeckiego Str., 50-345 Wroclaw, Poland

[2]Department of Medical Biochemistry, Wroclaw Medical University,
10, Chalubinskiego Str., 50-368, Wroclaw, Poland

[3]Department of Molecular and Cellular Biology, Wroclaw Medical University,
211A, Borowska Str., 50-556, Wroclaw, Poland

*E-mail address: stkwiatek@gmail.com

ABSTRACT

Malignant melanoma is a highly invasive cancer which derives from neuroectodermic melanocytic cells. It is characterized by the highest frequency of cases in both sexes and all age groups. High metastatic potential of melanoma and its multidrug resistance might be a significant problem in the treatment. Permanent and complete remissions are rare, while the 5-year survival rate remains relatively low. In the last years there has been a breakthrough in the systemic therapy of malignant melanoma. Modern drugs have revolutionized previous therapeutic management of melanoma. As part of therapeutic programs, new medicines are available: dabrafenib, ipilimumab, pembrolizumab, trametinib and vemurafenib. The following paper presents current clinical management standards for melanoma diagnoses, based on the widely accepted scientific data and expert experience - with emphasis on modern methods of treatment of this cancer.

***Keywords*:** melanoma, melanoma staging, AJCC, dabrafenib, ipilimumab, pembrolizumab, vemurafenib, *Melanoma malignum*, photodynamic therapy, electrochemotherapy

(Received 27 May 2018; Accepted 14 June 2018; Date of Publication 15 June 2018)

1. INTRODUCTION

Malignant melanoma (latin: *Melanoma malignum*) is a highly invasive cancer which derives from neuroectodermic melanocytic cells [1]. It is characterized by the highest frequency of cases in both sexes and all age groups. In Poland, the number of patients raised threefold in 1980-2010, reaching a level of 2.500 new diagnosed people per year. Permanent and complete remissions are rare, while the 5-year survival rate remains relatively low [2]. High metastatic potential of melanoma and its multidrug resistance might be a significant problem in the treatment. According to the above, it is justified to quest for new, effective methods of anti-melanoma therapy.

In the last years there has been a breakthrough in the systemic therapy of malignant melanoma. New methods of both molecular-targeted treatments and immunotherapy were developed. Modern drugs have revolutionized previous therapeutic management of melanoma. As part of therapeutic programs, new medicines are available: dabrafenib, ipilimumab, pembrolizumab, trametinib and vemurafenib [3].

The following paper presents current clinical management standards for melanoma diagnoses, based on the widely accepted scientific data and expert experience - with emphasis on modern methods of treatment of this cancer.

2. MELANOMA ETIOPATHOGENESIS

Melanoma is a malignant tumor that originates from skin melanocytes, mucous membranes or uveal layer of the eyeball. Due to the high metastatic potential of the tumor, determining its primary localization is sometimes very difficult and impossible. Etiological factors leading to malignant transformation of normal melanocytes have not been fully understood. The predisposition to the developing skin cancers is associated with a dose of ultraviolet radiation (UV) that exerts mutagenic effects on nuclear DNA. People with a bright skin phenotype (type I or II) are particularly vulnerable to harmful UV effects. The type and intensity of exposure also play an important role. The use of solarium (high doses of UV-A and UV-B in a short time) increases the risk of melanoma almost twice [4]. For this reason, many countries have excluded the use of solarium: totally (Brazil) or for underage (Poland, Germany) [5]. Risk factors also include individual propensity to sunburn, as well as severe sunburns in adolescence (twice or threefold increase the risk after 5 burn episodes).

An important role in preventing the development of melanoma and other neoplastic processes is associated with the proper condition of the immune system. The decrease of cell-mediated and humoral immune responses, as well as disturbances in the integrity of organism's natural defense barriers favor the growth of proliferation processes. UV radiation (especially UV-B) impairs the defense mechanisms of the skin, promoting the formation of oxidized melanin, which causes additional damage of DNA and inhibits apoptosis. Furthermore, the increased risk of melanoma in patients with immunosuppression is emphasized: after organs transplantations or patients with AIDS (*acquired immune deficiency syndrome*) [5].

Carcinogenesis may occur on the genetic level [6][7]. Mutations in the following genes such a CDKN2A [8], TP16/CDK4 [9], TP14, BRAF V600E [10], and TP53 [11] play an important role in the pathogenesis of melanoma [12]. Genetic load (one first stage relation

with patient suffering from melanoma) increase the risk of the skin cancer at least 3 times [12]. We cannot fail to mention the *Familial atypical multiple mole melanoma* (FAMMM) syndrome which is an autosomal dominant hereditary disorder [13] associated with CDKN2A mutation [8]. Penetration of mutation is even to 92% in melanoma-prone families [8][14][13].

3. CLINICAL SYMPTOMS

Skin melanoma may develop *de novo* (within the skin previously unchanged) or based on the pigmentary nevi:

- melanocytic lesions - arise as a result of developmental abnormalities of the skin during fetal life (dysplastic, melanocytic, congenital),
- pigment stains.

Melanoma in the early stage of growth is a flat, asymmetrical, multi-colored change with irregular borders. Over time, it emphasizes over the skin level, creating ulcers with blood exudate on the surface [15].

Clinical symptoms of melanoma are grouped in the ABCDE clinical system, aimed at facilitating the diagnosis of cancer (Table 1) [16].

Table 1. Clinical picture of cutaneous melanomas in the ABCDE system [16].

A (*assymetrical shape*)	Melanoma is asymmetric in every axis, presents irregular shape (to distinguish: benign changes are usually round or oval).
B (*borders*)	The edges are jagged and uneven.
C (*color*)	• Usually from light brown to black, • sometimes white, red or blue, • irregular dye distribution.
D (*diameter*)	Usually greater than 6 mm (*the size of a pencil eraser*), perceptible dynamics of morphological changes.
E (*elevation or evolution/change*)	The mole's surface above the level of the epidermis surrounding the tumor

Some authors in the above classification also include the feature "*F*", which means "funny looking". It refers to the prophylactic "*ugly duckling rule*" according to which, the patient observing his skin should pay special attention to the nevi that stand out in shape, color or size from other moles. The "*funny looking mole*", like the "*ugly duckling sign*" implies that there is an overall suspect [17].

As the disease progresses, melanoma infiltrates the deeper layers of the skin, producing metastases in the vicinity of the primary focus, to the lymph nodes as well as distant metastasis through the lymph and blood vessels (mainly lungs, liver, brain and bones) [18].

4. DIAGNOSTICS

The most crucial element of early diagnosis of melanoma is a thorough examination of the patient's skin (in good light), which must also include areas that are difficult to access - scalp, hands and soles of the feet, interdigital spaces, genital and anal areas. Physician should remember about the possibility of presence subungual melanoma, on mucous membranes (for example vulva), as well as the uveal type.

Dermatoscopy (epiluminescence microscopy) is used in the initial diagnosis. This method reaches 96.3% of sensitivity and 94.2% of specificity. This is a non-invasive method and the standard test takes several minutes. Lesions are viewed under a standardized source of light, approximately 20x magnified, which allows their further objective assessment by the doctor [19].

To confirm the diagnosis and determine the stage of cancer, histopathological examination of the entire surgically cut pigmented lesion is necessary. The suspected skin lesion is dissected with a margin of healthy skin, and if the diagnosis of melanoma is established - a possible decision to widen the excision is made [20].

Patients with infiltration exceeding 1 mm are classified for sentinel lymph node biopsy (SLNB). It is a method which is necessary to evaluate the presence of micrometastases in the lymph nodes. Sentinel node biopsy is performed after dissecting biopsy of melanoma using lymphoscintigraphy. SNLB is characterized by low incidence of postoperative complications, therefore it is considered to be a minimally invasive diagnostic method [21].

After determining the histopathological diagnosis and assessment of the presence of metastases in regional lymph nodes, the treatment should be implemented in accordance to the evaluation of the cancer stage. Currently, the melanoma classification system is based on the TNM (*tumor, lymph nodes, metastasis*) scale of the American Joint Committee on Cancer (AJCC – 8th edition, 2017) (Table 2, 3, 4) [22].

Table 2. Melanoma classification for diagnosis. T (primary tumor), N (regional lymph nodes) and M (distant metastasis) categories.

(Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017: 563–585) [22]

T CATEGORY	THICKNESS [mm]	ULCERATION STATUS
Tx (primary tumor thickness cannot be assessed)	Not applicable	Not applicable

T0 (no evidence of primary tumor)		Not applicable	Not applicable
Tis (melanoma *in situ*)		Not applicable	Not applicable
T1a		<0,8 mm	Without ulceration
T1b		<0,8 mm	With ulceration
		0,8 mm – 1 mm	With or without ulceration
T2a		1,0 – 2,0 mm	Without ulceration
T2b		1,0 – 2,0 mm	With ulceration
T3a		2,0 – 4,0 mm	Without ulceration
T3b		2,0 – 4,0 mm	With ulceration
T4a		> 4,0 mm	Without ulceration
T4b		< 4,0 mm	With ulceration
N CATEGORY		**No. OF INVOLVED REGIONAL LYMPH NODES**	**PRESENCE OF IN-TRANSIT, SATELLITE AND/OR MICROSATTELITE METASTESES**
Nx		Regional nodes not assessed	No
N0		0 (no regional metastases detected)	No
N1	N1a	One clinically occult (ie, detected by SNL biopsy)	No
	N1b	One clinically detected	No
	N1c	No regional lymph node disease	Yes
N2	N2a	Two or three clinically occult	No
	N2b	Two or three, at least one which was clinically detected	No
	N2c	One clinically occult or clinically detected	Yes

N3	N3a	Four or more clinically occult	No
	N3b	Four or more, at least one which was clinically detected, or the presence of any number of matted nodes	No
	N3c	Two or more clinically occult or clinically detected and/or the presence of any number of matted nodes	Yes
M CATEGORY		**ANATOMIC SITE**	**LDH LEVEL**
M0		No evidence of distant metastases	Not applicable
M1a		Distant metastasis to skin, soft tissue including muscles and/or non-regional lymph nodes	Not elevated [M1a(0)] or elevated [M1a(1)]
M1b		Distant metastasis to lung with or without M1a sites of the disease	Not elevated [M1b(0)] or elevated [M1b(1)]
M1c		Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not elevated [M1c(0)] or elevated [M1c(1)]
M1d		Distant metastasis to CNS with or without M1a-c sites of disease	Not elevated [M1d(0)] or elevated [M1d(1)]

Table 3. AJCC Pathological (pTNM) Prognostics Stage Groups

(Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563–585) [22]

PATHOLOGICAL STAGE GROUP	T CATEGORY	N CATEGORY	M CATEGORY
0	Tis	N0	M0
IA	T1a	N0	M0

	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1a/b – T2a	N1a, N2a	M0
IIIB	T0	N1b, N1c	M0
	T1a/b - T2a	N1b/c, N2b	M0
	T2b, T3a	N1a – N2b	M0
IIIC	T0	N2b, N2c, N3b, N3c	M0
	T1a – T3a	N2c, N3a/b/c	M0
	T3b, T4a	Any N ≥N1	M0
	T4b	N1a – N2c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

Table 4. AJCC Clinical (cTNM) Prognostic Stage Groups

(Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017: 563–585) [22]

CLINICAL STAGE GROUP	T CATEGORY	N CATEGORY	M CATEGORY
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0

IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T, Tis	≥N1	M0
IV	Any T	Any N	M1

Both, clinical and pathological classifications are used in malignant melanoma staging [23].

5. TREATMENT

The surgical treatment is the method of choice. The suspected pigmented lesion needs to undergo a excisional biopsy. The further cure (after histopathological confirmation of melanoma) depends on the clinical stage of cancer, according to the TNM scale.

5. 1. Stages I-II

The complete removal of the scar after biopsy of the primary focus is required. It is recommended to keep the border of healthy skin. For invasive melanomas with Breslow thickness ≤1 mm (Table 4), the recommended marginal clearance is 1cm of surrounding skin. For melanomas with a Breslow depth between 1 and 2 mm, surgical margins should take 1–2 cm. For melanomas between 2 and 4 mm in Breslow depth, as well as for the so-called "*thick melanomas*" margins of excision 2 cm are required [24][25].

Table 5. Breslow scale (according to TNM system)

(McCarter MD. "Melanoma" in "Abernathy's Surgical Secrets", Elsevier, 2009, pp. 328-335) [26]

BRESLOW STAGE	MELANOMA THICKNESS
I	≤ 1 mm
II	1 – 2 mm
III	2 – 4 mm
IV	> 4mm

5. 2. Stages III

5. 2. 1. Surgical management

The presence of metastases in regional lymph nodes is an important factor determining further prognosis in patients with cutaneous melanoma. If the presence of metastases in sentinel nodes or in clinically enlarged lymph nodes is confirmed, lymphadenectomy should be performed. Infiltration of melanoma cells beyond the lymph node capsule is an additional factor negatively affecting the patient's prognosis [27].

5. 2. 2. Treatment of metastases to subcutaneous tissue and *in-transit*

In-transit metastases (accompanying lymphatic vessels running from the tumor to the regional lymphatic system) should be removed surgically. In cases of multiple or unresectable changes, other forms of treatment should be considered: electrochemotherapy, radiotherapy, limb perfusion chemotherapy.

Electrochemotherapy (ECT) is a modern technique for the treatment of cancers located in the subcutaneous (localization in the skin or subcutaneous tissue) as well as internal tumors. This method involves the combination of local or systemic chemotherapy and application of ultra-short electrical pulses of high intensity to induce temporary tumor electropermeabilization. By using ECT, high doses of chemotherapeutics penetrate into permeabilized tumor cells whereas drug concentration is similar or even lower, than in standard treatment. The use of the reversible electroporation phenomenon leads to the increase in the effective concentration of cytostatic (e.g., intravenous bleomycin or intratumoral cisplatin) in tumor cells and a reduce of dose which is less toxic to healthy cells. Within, the tumor, fibrous lesions develop, and pathological cells undergo destruction. Electrochemotherapy is characterized by a high percentage of responses to treatment (over 80%). It is used mainly in the treatment of multiple cancerous metastases to the skin, which are not eligible for surgical treatment. The indications for ECT are primarily: melanoma and recurrent skin cancers, skin metastases of internal organs, dermatofibrosarcoma, angiosarcoma, head and neck cancer [28].

The extensive and multiple lesions, localized on the limb, can be treated by limb perfusion chemotherapy in hyperthermia (hyperthermic isolated limb perfusion - HILP). It is a regional chemotherapy technology, based on high doses of a cytostatic drug (melphalan or TNF-alpha) perfused to the limb isolated from the systemic circulation. It allows to achieve 10-100x higher concentrations of the drug in perfused tissue than after systemic administration of the cytostatics. The HILP method is used in the case of local recurrence (without distant metastases) of previously radically excised melanoma and unresectable in-transit metastases. Complications are rare and include penetration of cytostatic to the general circulation or limb amputation [29].

5. 2. 3. Adjuvant treatment

Adjuvant treatment of locally advanced melanoma should be considered in case of significantly thick lesions or with primary tumor’s ulceration (IIB / IIC stages). It is also indicated after removal of regional lymph nodes in patients exposed to relapse (grade III). Currently used methods of adjuvant therapy are: adjuvant radiotherapy and systemic treatment with the use of interferon alfa-2b. Adjuvant treatment reduces the number of local recurrences, however without affecting overall survival (OS). Clinical trials are being carried

out on the use in adjuvant therapy, including anti-CTLA-4 antibodies and drugs directed to the BRAF-MEK pathway [30].

5. 3. Treatment of metastatic malignant melanoma

Treatment of patients with stage IV of melanoma is constantly developing. New methods of systemic therapy have improved the overall survival of patients, reaching a period from 10-15 months [31]. The systemic treatment is essential for advanced stage of cancer, however the possibility of surgical excision of secondary lesions in the skin or distant metastases should always be considered - especially if they are sparse and concern one organ.

5. 3. 1. Chemotherapy

Currently, chemotherapeutic protocols allow for one cytostatic - dacarbazine, but its effectiveness is relatively low. The objective response of dacarbazine is observed in 10-15% of patients, with a total remission rate of only 5%. The median duration of the response is up to 4 months. The multidrug therapeutic procedures applied in the regimens containing dacarbazine (in combination with cisplatin, vinblastine, etc.) have not confirmed their efficacy [32].

5. 3. 2. Immunotherapy

The available clinical data, prove that, the use of interleukin 2 in monotherapy and in combination with interferon alfa-2b may insignificantly increase the treatment index, however it severe the side effects and without positive impact on overall survival of patients [33].

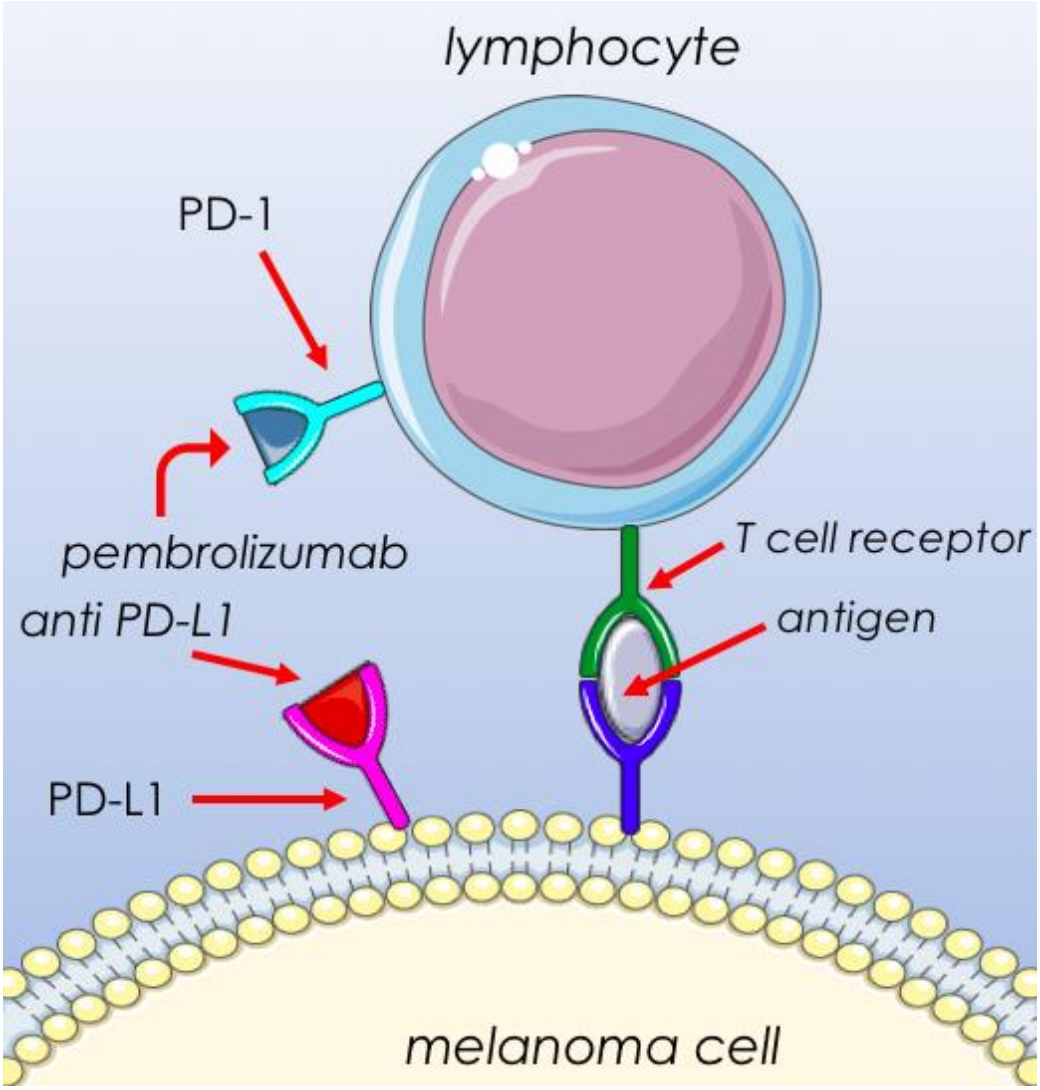
5. 3. 3. Ipilimumab

Ipilimumab was the first medicine, which significantly extended the overall survival among the patients suffering from melanoma [34][35]. It's the human recombinant monoclonal antibody, which is the blocker of antigen CTLA-4 [36], which occur on activated lymphocytes T membranes surface [37] and inhibits the lymphocyte response [38]. Owing to that fact, the treatment with ipilimumab results in stimulation of immune system expressed in intensified attack the tumour cell by lymphocytes [35]. Activated lymphocytes T through cytotoxicity mechanism and cytokines secretion cause apoptosis of melanoma cells [39]. The study of Zaragoza et al. revealed that the increase in absolute lymhocyte count – ALC was observed during the ipilimumab mediated therapy [40].

This agent is used especially in unresectable or metastatic skin melanoma treatment [40]. Despite of the fact that percentage of objective responses during ipilimumab therapy oscillates about 10%, there is observed significant extension of life [40]. Moreover, Schadendorf et al. studies exposed that in the group of 1861 patient with melanoma, threated with ipilimumab, the median of overall survival was 11,4 months, and the percentage of 3 years survival was 22%). Longer survival rate was obtained at patients suffering from melanoma, who had not received systemic treatment before (the median of overall survival was 13,5 months, and the percentage of 3 years survival was 20%) [41].

5. 3. 4. Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody blocking the programmed cell death receptor (*programmed cell death protein 1* - PD-1). PD-1 is a glycoprotein receptor that is presented primarily on activated T and B lymphocytes. It is one of the most important negative regulators of the immune response, which is responsible for preventing the development of autoimmune diseases and controlling damage of healthy tissue during infection. PD1 receptor ligand - PD-L1 (*programmed death ligand 1*) is located on the surface of almost all human cells. Tumor cells express PD-L1 ligand or stimulate PD-1 receptor expression in lymphocytes, thereby inhibiting the anti-tumor response. Increased expression of the PD-L1 ligand was showed on the surface of melanoma cells (Scheme 1).



Scheme 1. Mechanism of action of *anti PD-1* and *anti PD-L1* antibodies.

(Modified from: National Cancer Institute website, https://www.cancer.gov/news-events/cancer-currents-blog/2015/pembrolizumab-nsclc and Servier Medical Art website, http://smart.servier.com/)

The inhibitor of PD-L1 ligand is atezolizumab – antibody which is used in the therapy of lung cancer. However, any mechanisms have not been identified whereby tumor cells induce expression of PD-L1 or PD-1 on lymphocytes infiltrating cancer.

The previous studies on anti-PD-1 antibodies have indicated their high efficacy in the treatment of melanoma and non-small cell lung carcinoma (NSCLC). Pembrolizumab is used in particular among patients with non-surgical or spread melanoma, without mutations in the BRAF gene. In the study conducted by Robert et al., a group of 843 patients with advanced melanoma without prior systemic treatment were assigned in a 1: 1: 1 ratio to the pembrolizumab group at a dose of 10 mg / kg BW every 2 weeks, to the group treated with the same dose of pembrolizumab every 3 weeks and to the ipilimumab group (4 doses of 3 mg / kg every 3 weeks). The response rate was the highest in the pembrolizumab group every 2 weeks (33.7%), then every 3 weeks (32.9%), and the lowest ones treated with ipilimumab - 11.9%. The estimated 12-month survival rates were 74.1%, 68.4% and 58.2%, respectively. In conclusion, pembrolizumab has been shown to be more effective, than ipilimumab in the first line of melanoma treatment. The results of the therapy were similar when using the drug every 2 and every 3 weeks [42].

In case of the treatment with pembrolizumab, increased risk of pseudo-aggression occurrence has been occured. This phenomenon is characterized as an increase in the size of treated lesions or the appearance of new lesions in the first phase of treatment. It is related to the infiltration of inflammatory cells in the neoplastic area, which is an expected phenomenon. These changes regress during further treatment [43].

5. 3. 5. Vemurafenib

Approximately half of melanoma tumors are BRAF positive (), and more than 90% of them are BRAF-V600E positive [10] – which means that these tumor cells show specific missunderstanding mutation in codon V600E, which is responsible for activating BRAF kinase. It leads to permanent hyperactivity of the kinase and lack of sensitivity to feedback signals inhibiting its enzymatic activity. As a result, in this melanoma cells there is a disturbance of the process of apoptosis, increase of the replication potential of the tumor and avoidance of the immune response [44]. Hugdahl et al. revealed that positive BRAF-V600E expression is significantly associated with malignancy [45]. Moreover, BRAF V600E mutations affect tumor angiogenesis by stimulating the secretion of vascular endothelial growth factor (VEGF) [44].

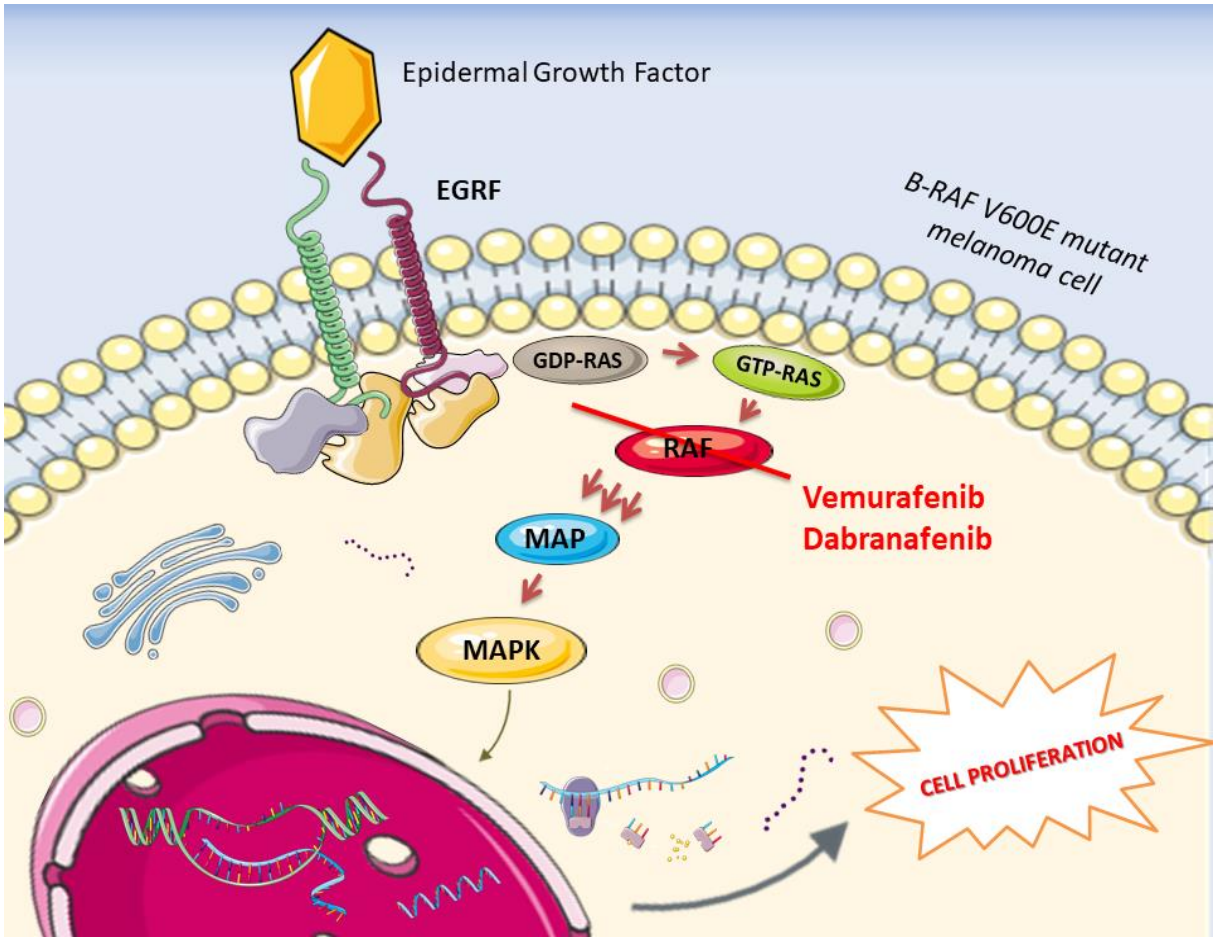
In recent years, vemurafenib has become an interesting alternative for classic treatment in BRAF positive melanomas [46]. Vemurafenib is a selective kinase inhibition of the mitogen activated protein kinase (MAPK) pathway in patients with BRAF mutation [47] (scheme 2). BRAF protein is an integral part of the intracellular signalling pathway RAS-RAF-MEK-ERK, which is associated with proliferation, differentiation and growth of cells. Signalling pathway RAS-RAF-MEK-ERK is being activated by extracellular growth factors like: fibroblast growth factor – FGF, hepatocyte growth factor – HGF and stem cell factor – SCF. After activation of this pathway, the RAS protein stimulates serine-threonine BRAF kinase, which starts mitogen activated protein kinase – MAPK. The MAP kinase which the sequence was last described, affects directly on transcription factors, accelerating cell proliferation [48].

Blockade of MEK phosphorylation by vemurafenib in RAS-RAF-MEK-ERK signalling pathway leads to the decrease in melanoma cell proliferation and potentiate apoptosis. Before

initiating vemurafenib therapy, the presence of BRAF mutations should be confirmed by appropriate genetic tests. Sosman et al. studies have exposed that Vemurafenib is usually well tolerated however, some limitations associated with serious specific side effects like: skin toxicity, joint pain, and cardiotoxicity has been revealed [49], as well as the increasing resistance to this medicine [50].

5. 3. 6. Dabrafenib

Dabrafenib is reversible, ATP-competitive BRAF inhibitor (scheme 2). This agent expose similar mechanism of effectiveness and side effects to Vemurafenib. Among patients suffering from advanced melanoma with BRAF V600E mutations, who had resided dabrafenib as a first treatment - the median of progression-free survival was 6.7 months. The median of overall survival after a year, the median of overall survival 18.2 months was reported [51].



Scheme 2. Vemurafenib and dabrafenib mechanism of action.

(Modified from: R. Fisher and J. Larkin, "Vemurafenib: a new treatment for BRAF-V600 mutated advanced melanoma." *Cancer Manag. Res.*, vol. 4, pp. 243–52, 2012 [48], and: Servier Medical Art website, http://smart.servier.com/)

6. CONCLUSIONS

In recent years, clinical management of malignant melanoma has evolved considerably. New drugs that inhibit the development of cancer are being studied, and research is under way to improve the current therapies. Systematic administration of modern molecular-targeted drugs and improving the function of the immune system significantly have increased the percentage of total remissions. Photodynamic therapy and electrochemotherapy may become interesting alternative for patients not qualified to surgery or systemic chemotherapy. The conducted considerations give hope for further progress in the treatment of patients with malignant skin tumors.

References

[1] Erdei E, Torres SM. A new understanding in the epidemiology of melanoma. *Expert Rev. Anticancer Ther.* 10(11) (2010) 1811–23.

[2] Krajowy Rejestr Nowotworów, Dane Statystyczne - Czerniak skóry (C43). [Online]. Available: http://onkologia.org.pl/czerniak-skory-c43/. [Accessed: 01-Apr-2018].

[3] Iams WT, Sosman JA, Chandra S. Novel Targeted Therapies for Metastatic Melanoma. *Cancer J.* 23(1) (2017) 54–58.

[4] Tucker MA, Goldstein AM. Melanoma etiology: where are we? *Oncogene* 22(20) (2003) 3042–3052.

[5] Kubica AW, Brewer JD. Melanoma in immunosuppressed patients. *Mayo Clin. Proc.* 87(10) (2012) 991–1003.

[6] Bommer UA, Vine KL, Bommer U. Cancer biology: molecular and genetic basis "Chapter 3 -Cancer Biology: Molecular and Genetic Basis."

[7] Drewa G, Powierska-Czarny J. Genetic basis of malignant melanoma. *Postepy Hig. Med. Dosw.* vol. 52(4) (1998) 367–80.

[8] Eckerle Mize D, Bishop M, Resse E, Sluzevich J. *Familial Atypical Multiple Mole Melanoma Syndrome*. National Center for Biotechnology Information (US), 2009.

[9] Piccinin S, Doglioni C, Maestro R, Vukosavljevic T, Gasparotto D, D'Orazi C, Boiocchi C. p16/CDKN2 and CDK4 gene mutations in sporadic melanoma development and progression. *Int. J. cancer* 74(1) (1997) 26–30.

[10] Ascierto PA, Kirkwood JM, Grob JJ, Simeone E, Grimaldi AM, Maio M, Palmieri G, Testori A, Marincola FM, Mozzillo N. The role of BRAF V600 mutation in melanoma. *J. Transl. Med.* 10 (2012) 85.

[11] Weiss J, Heine M, Arden KC, Korner B, Pilch H, Herbst RA, Jung EG. Mutation and expression of TP53 in malignant melanomas. *Recent Results Cancer Res.* 139 (1995) 137–54.

[12] Rastrelli M, Tropea S, Rossi CR, Alaibac M. Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. *In Vivo* 28(6) (2014) 1005–11.

[13] Czajkowski R, Placek W, Drewa G, Czajkowska A, Uchańska G. FAMMM syndrome: pathogenesis and management. *Dermatol. Surg.* 30(2) (2004) 291–6.

[14] Parker JF, Florell SR, Alexander A, DiSario JA, Shami PJ, Leachman SA. Pancreatic Carcinoma Surveillance in Patients With Familial Melanoma. *Arch. Dermatol.* 139(8) (2003) 1019.

[15] Vyas R, Selph J, Gerstenblith MR. Cutaneous manifestations associated with melanoma. *Semin. Oncol.* 43(3) (2016) 384–389.

[16] Abbasi NR, Shaw HM, Rigel DS, Friedman RJ, McCarthy WH, Osman I, Kopf AW, Polsky D. Early Diagnosis of Cutaneous Melanoma. *JAMA* 292(22) (2004) 2771.

[17] Daniel Jensen J, Elewski BE. The ABCDEF Rule: Combining the "ABCDE Rule" and the "Ugly Duckling Sign" in an Effort to Improve Patient Self-Screening Examinations. *J. Clin. Aesthet. Dermatol.* 8(2) (2015) 15.

[18] Zbytek B, Carlson JA, Granese J, Ross J, Mihm MC Jr, Slominski A. Current concepts of metastasis in melanoma. *Expert Rev. Dermatol.* 3(5) (2008) 569–585.

[19] Situm M, Buljan M, Kolić M, Vučić M. Melanoma - clinical, dermatoscopical, and histopathological morphological characteristics. *Acta Dermatovenerol. Croat.* 22(1) (2014) 1–12.

[20] Krathen M. Malignant Melanoma: Advances in Diagnosis, Prognosis, and Treatment. *Semin. Cutan. Med. Surg.* 31(1) (2012) 45–49.

[21] Beasley GM, Hu Y, Youngwirth L, Scheri RP, Salama AK, Rossfeld K, Gardezi S, Agnese DM, Howard JH, Tyler DS, Slingluff CL Jr, Terando AM. Sentinel Lymph Node Biopsy for Recurrent Melanoma: A Multicenter Study. *Ann. Surg. Oncol.* 24(8) (2017) 2728–2733.

[22] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, Meyer L, Gress DM, Byrd DR, Winchester DP. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more 'personalized' approach to cancer staging. *CA. Cancer J. Clin.* 67(2) (2017) 93–99.

[23] Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA. Cancer J. Clin.* 67(6) (2017) 472–492.

[24] Danialan R, Gopinath A, Phelps A, Murphy M, Grant-Kels JM. Accurate identification of melanoma tumor margins: a review of the literature. *Expert Rev. Dermatol.* 7(4) (2012) 343–358.

[25] Riker AI, Kirksey L, Thompson L, Morris A, Cruse CW. Current surgical management of melanoma. *Expert Rev. Anticancer Ther.* 6(11) (2006) 1569–83.

[26] McCarter MD. "Melanoma" in *Abernathy's Surgical Secrets*. Elsevier, (2009) 328–335.

[27] Mun GH. Management of malignant melanoma. *Arch. Plast. Surg.* 39(5) (2012) 565–74.

[28] Bigi L, Galdo G, Cesinaro AM, Vaschieri C, Marconi A, Pincelli C, Fantini F. Electrochemotherapy induces apoptotic death in melanoma metastases: a histologic and

immunohistochemical investigation. *Clin. Cosmet. Investig. Dermatol.* 9 (2016) 451–459.

[29] Raymond AK, Beasley GM, Broadwater G, Augustine CK, Padussis JC, Turley R, Peterson B, Seigler H, Pruitt SK, Tyler DS. Current trends in regional therapy for melanoma: lessons learned from 225 regional chemotherapy treatments between 1995 and 2010 at a single institution. *J. Am. Coll. Surg.* 213(2) (2011) 306–16.

[30] Davar D, Kirkwood JM. Adjuvant Therapy of Melanoma. *Cancer treatment and research* 167 (2016) 181–208.

[31] Song X, Zhao Z, Barber B, Farr AM, Ivanov B, Novich M. Overall survival in patients with metastatic melanoma. *Curr. Med. Res. Opin.* 31(5) (2015) 987–991.

[32] Ugurel S, Paschen A, Becker JC. Dacarbazine in Melanoma: From a Chemotherapeutic Drug to an Immunomodulating Agent. *J. Invest. Dermatol.* 133(2) (2013) 289–292.

[33] Petrella T, Quirt I, Verma S, et al. Single-agent interleukin-2 in the treatment of metastatic melanoma: a systematic review. *Cancer Treat. Rev.* 33(5) (2007) 484–96.

[34] Jason F, Luke J. Is There an Optimal Dose of Ipilimumab in Melanoma? ASCO Annual Meeting. *ASCO Daily News*, 2017.

[35] Tarhini A, Lo E, Minor DR. Releasing the brake on the immune system: ipilimumab in melanoma and other tumors. *Cancer Biother. Radiopharm.* 25(6) (2010) 601–13.

[36] Lipson EJ, Drake CG. Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma. *Clin. Cancer Res.* 17(22) (2011) 6958–62.

[37] McCoy KD, Le Gros G. The role of CTLA-4 in the regulation of T cell immune responses. *Immunol. Cell Biol.* 77(1) (1999) 1.

[38] Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, Linsley PS, Thompson CB, Riley JL. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Mol. Cell. Biol.* 25(21) (2005) 9543–53.

[39] Camacho LH. CTLA-4 blockade with ipilimumab: biology, safety, efficacy, and future considerations. *Cancer Med.* 4(5) (2015) 661–72.

[40] Zaragoza J, Caille A, Beneton N, Bens G, Christiann F, Maillard H, Machet L. High neutrophil to lymphocyte ratio measured before starting ipilimumab treatment is associated with reduced overall survival in patients with melanoma. *Br. J. Dermatol.* 174(1) (2016) 146–151.

[41] Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, Patt D, Chen TT, Berman DM, Wolchok JD. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. *J. Clin. Oncol.* 33(17) (2015) 1889–1894.

[42] Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. *N. Engl. J. Med.* 372(26) (2015) 2521–2532.

[43] Khoja L, Butler MO, Kang SP, Ebbinghaus S, Joshua AM. Pembrolizumab. *J. Immunother. Cancer*. 3(1) (2015) 36.

[44] Sharma A, Shah SR, Illum H, Dowell J. Vemurafenib. *Drugs* 72(17) (2012) 2207–2222.

[45] Hugdahl E, Kalvenes MB, Puntervoll HE, Ladstein RG, Akslen LA. BRAF-V600E expression in primary nodular melanoma is associated with aggressive tumour features and reduced survival. *Br. J. Cancer* 114(7) (2016) 801–8.

[46] Knapen LM, Koornstra RHT, Driessen JHM, et al. The Impact of Dose and Simultaneous Use of Acid-Reducing Agents on the Effectiveness of Vemurafenib in Metastatic BRAF V600 Mutated Melanoma: a Retrospective Cohort Study. *Target. Oncol.* Apr. 2018.

[47] Zecena H, Tveit D, Wang Z, et al. Systems biology analysis of mitogen activated protein kinase inhibitor resistance in malignant melanoma. *BMC Syst. Biol.* 12(1) (2018) 33.

[48] Fisher R, Larkin J. Vemurafenib: a new treatment for BRAF-V600 mutated advanced melanoma. *Cancer Manag. Res.* 4 (2012) 243–52.

[49] Johnson DB, Sosman JA. Therapeutic Advances and Treatment Options in Metastatic Melanoma. *JAMA Oncol.* 1(3) (2015) 380.

[50] Telang S, O'Neal J, Tapolsky G, Clem B, Kerr A, Imbert-Ferndandez Y, Chesney J. Discovery of a PFKFB3 inhibitor for phase I trial testing that synergizes with the B-Raf inhibitor vemurafenib. *Cancer Metab.* 2(1) (2014) P14.

[51] Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 380(9839) (2012) 358–365.