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## Current prospects of successful therapeutic procedures in advanced stage melanoma – the short review

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### Summary:

**Introduction and purpose:** Melanoma is the most aggressive form of skin cancer with a rapid course of disease in advanced stage according to the melanoma staging system of the American Joint Committee on Cancer (AJCC). Its morbidity has increased from 20<sup>th</sup> century. Intermittent sun exposure, age and skin phenotype are included into main risk factors of melanoma. The gold standard in diagnostic and therapeutic procedures is the naevus excisional biopsy associated with histopathology examination. The knowledge about immune system and melanoma biology have enabled therapeutic advantages, such as immunotherapy and molecular target therapy.

**Objective:** To review currently available data on PubMed about current prospects of successful therapeutic procedures in advanced stage melanoma.

**A brief description of the state of knowledge:** A systemic complementary therapy and non-specific immunotherapy are used for treatment advanced-stage-melanoma patients. Current knowledge has enabled an implementation of molecular target therapy in advanced stage melanoma. Evidence based science has yielded promising results and it has included these therapies to the clinical practice, especially molecular target therapy and immunotherapy as well. BRAF inhibitors including vemurafenib, dabrafenib and MEK inhibitors including trametinib are considered to medicaments, that have molecular mechanism of action. Nivolumab, pembrolizumab, ipilimumab are examples of monoclonal antibodies, which are used as an immunotherapy.

**Conclusions:** Excisional biopsy associated with histopathology have been an essential element in therapeutic and diagnostic procedures. Current achievements of medicine sciences have shed light on biology and pathogenesis highlighting the role of immunotherapy and molecular target treatment as well.

**Key words:** melanoma; naevus; ultraviolet radiation; molecular target treatment; immunotherapy;

## Article

### 1. Introduction:

Melanoma morbidity has increased from 20<sup>th</sup> century. [1] According to American Institute for Cancer Research there were nearly 300 000 new cases in 2018 and it is in the 19<sup>th</sup> place among occurring cancer in male and female in the world. [2] In Poland melanoma was presented in ca. 2,2 – 2,4 % cases of malignancy and it is cause ca. 1% of cancer mortality.[3] 5-year survival rate is depended on severity of disease and it equals approximately 20-30 % in 4-stage-melanoma, even though a systemic treatment was used. [4]

Melanoma is a multi-factorial disease, including: interaction between environmental exposure, age, skin phenotype and genetic mutations. [4] The most important modifiable risk factor is sunlight associated with ultraviolet radiation (UV), especially UV B spectrum. [5, 6] Intense and intermittent sun exposure (typical of sunburn history) may have harmful consequences particularly. [6] UV B rays can due to principal DNA lesions lead to DNA mutations whose contribute oncogenesis. [7] Evidence based knowledge suggests, that approximately 25 % of melanoma cases arise on pre-existing naevus. [6, 8]

The gold standard in diagnostic and therapeutic procedures is naevus excisional biopsy associated with histopathology examination. Consequently, determining histologic diagnosis and predictors as well tumor thickness measurement according to Breslow scale are used for planning further treatment. [4, 9] It seems, that owing to the current state of knowledge about target therapy implementation in metastatic melanoma, overall survival factor and prognosis have been increased. [9, 10]

### Objective

The purpose of this manuscript is elaborating currently available data on PubMed about current prospects of treatment in advanced stage melanoma especially molecular therapy and immunotherapy.

## **2. State of knowledge:**

Surgical excision of melanoma is the routine treatment standard as well as histopathology. Further therapeutic procedure is depended on microscopical examination. Infiltration thickness, Ki-67 expression, lesions ulceration, metastasis (especially to lymph nodes) and high LDH level, which may be negative prognostic factors. [4] They determine if lymphadenectomy or systemic treatment will be a necessity.

Systemic complementary therapy and non-specific immunotherapy are used for treatment advanced-stage-melanoma patients. It contains BRAF inhibitors (vemurafenib, dabrafenib) and MEK inhibitors (trametinib). Nivolumab, pembrolizumab, ipilimumab are examples of monoclonal antibodies which are used as an immunotherapy.

### **2.1 Molecular target therapy in metastatic melanoma**

Genomic alterations including genes that control: proliferation (BRAF, NRAS, NF1) growth and metabolism (PTEN and proto-oncogene receptor tyrosine kinase - KIT), resistance to apoptosis (TP53), cell cycle (cyclin-dependent kinase inhibitor 2A - CDKN2A) and replicative lifespan (telomerase reverse transcriptase - TERT) may lead to aberrant activation of the RAS/RAF/MEK/ERK cascade and the pathway of phosphoinositol-3-kinase (PI3K)/AKT (known as MAPK pathway). [7, 11] MAPK (mitogen-activated protein kinase) signal transduction pathway is involved in regulation of gene expression. Nearly 90 % melanoma reveal MAPK alterations. [7, 12] The most frequent of gene mutations, responsible for aberrant MAPK pathway, is BRAF mutation. It is observed in approximately 60 % of cases in intermittent sun-exposure related melanoma. [13] Since 2011 advanced stage melanoma treatment has been revolutionized with molecular target therapy, including selective BRAF inhibitors (as well vemurafenib and dabrafenib) and MEK kinase inhibitors (such as cobimetinib and trametinib). They have shown promising results, comparatively with dacarbazine, which was used previously. BRAF inhibitors revealed increasing overall survival (OS) and progression - free survival – (PFS). [14, 15] COMBI-d, COMBI-v, coBRIM i COLUMBUS studies for patients with metastatic melanoma have revealed that combination of MEK kinase and BRAF inhibitors (dabrafenib and trametinib, vemurafenib and cobimetinib) may have beneficial effect combined to the monotherapy. Combination of MEK and BRAF inhibitors extended overall survival and progression - free survival. The median OS was 23-33 months and median PFS was 12 – 14 months. [7]

### **2.2 Immunotherapy**

In 2018 James P. Allison and Tasuku Honjo were given a Nobel Prize in Physiology or Medicine for their discovery of melanoma therapy by inhibition of negative immune regulation. Crucial role in melanoma immunological response of CTLA-4 (cytotoxic T cell antigen 4), PD-1 (programmed-cell death protein) and PD-L1 (programmed-cell death ligand) was established. [16] These molecules are superficial proteins of antibody presented cells (APC) and T lymphocytes and they are included into points of negative immune regulation. Suppression of T-cell receptor (TCR) signaling and prevention of immunological hyperactivity, which would lead to cells injury, are the aim of this inhibitory mechanism. Immunotherapy against CTLA 4, PD1 and PD-L1 inhibits the negative immune regulation and induces lymphocyte cytotoxic activity towards melanoma cells. [17]

Physiologically, cells use PD1 and PD-L1 or CTLA4 activation pathway of negative immune regulation to prevent autoimmunization. These mechanisms are used for melanoma immune escape in case of growing neoplasm process. [17, 18] Melanoma microenvironment significantly influences immunosurveillance increasing tumor immunogenic profile. In this kind of neoplasm, cancer cells are infiltrated by lymphocytes, thus melanoma immunogenicity is revealed. [17] These indicate the effectiveness of immunotherapy.

Recombinant monoclonal antibodies are also known as immune checkpoints inhibitors and contain: ipilimumab (against CTLA 4), nivolumab and pembrolizumab (against PD 1) and atezolizumab, avalumab and durvalumab (against PD L1). Immunotherapy in advanced stage melanoma has provided effective and sustainable responses to treat III B and IV stage melanoma patients. The treatment with nivolumab or pembrolizumab significantly increased over 2 years. [7] Clinical study demonstrated that combination of monoclonal antibodies against CTLA 4 with against PD 1 or combination of immunotherapy with molecular target therapy as well as BRAF or MEK inhibitors seem to have beneficial role in treatment in advanced stage melanoma. [7, 19] Early results from the combination of atezolizumab (an anti-PD-L1 monoclonal antibody) and vemurafenib show promising positive activity against melanoma cells.

A promising method of immunotherapy is using the oncolytic virus, Talimogene laherparepvec (also known as T-VEC), which can cause tumor cell lysis. However, further studies should enforce its possible usefulness. [19, 20]

### **3. Conclusions:**

Intermittent high dose exposures increase risk of melanoma and number of genomic alterations; therefore, protection from the sun plays a crucial role in primary prevention of the carcinogenesis. It is an obviousness, that surgical resections interconnected with histopathology have been essential element in therapeutic and diagnostic procedures. Current achievements of medicine sciences have shed light on biology and pathogenesis highlighting the role of immunotherapy and target treatment as well. Elaborated studies have enabled establishing effective therapeutic strategies, that can prolong life of patients suffer from advanced stage melanoma more than a few months.

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