Review paper

Novel therapies for advanced skin carcinomas

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Abstract

Advanced skin carcinomas are a serious therapeutic problem. The statistical analysis shows a continuous increase in the incidence of both melanoma and non-melanoma skin cancers. Traditional therapies are characterized by low effectiveness and patients overall survival is not affected by them. By understanding the molecular pathways that lead to the neoplastic transformation and thanks to the knowledge of the immune system, it is possible to use personalized medicine in novel therapies for advanced skin carcinomas.

Key words: squamous cell carcinoma, basal cell carcinoma, melanoma, targeted therapy, immunotherapy.

Introduction

Cutaneous carcinomas are some of the most common cancers in the world. In the last few years, the incidence of skin cancer has increased globally. Skin cancers can be divided into cutaneous melanoma and non-melanoma skin cancers (NMSC), most of which are squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [1]. SCC and BCC are rarely malignant, therefore the available treatment options are limited [2]. On the other hand, although skin melanoma cases are reported far less, it is the most aggressive of all skin cancers and prone to advancing. Due to the low efficacy of traditional therapies, new treatments for advanced skin cancers are required [3, 4].

Molecular analysis of neoplastic changes created an opportunity for the development of modern drugs, the action of which, in many cases, is based on the inhibition of the activity of specific proteins – molecular targets. Several of the new drugs have been approved by the American Food and Drug Administration (FDA). However, many of them are in the phase of clinical trials aimed at determining the effectiveness of drugs as well as the selection of safe doses so as to minimize side effects [3, 4].

NMSCs are among the most widespread skin carcinomas; they constitute up to 96% of all skin cancers in the general population [1]. Studies carried out in the USA have shown that of all NMSCs reported, the number of BCCs is around 70–80%, and patients with SCC account for the remaining 20% of cases [2].

The increase in the incidence in the Caucasian population made melanoma the most common cancer among people with a fair skin type. Studies conducted in the USA have shown that melanoma is the fifth most common cancer in men and the sixth in women [5].

The aim of this review is to provide a new perspective on advanced SCC, BCC and melanoma cancer treatment with a special emphasis on personalized therapy and immunotherapy.

Squamous cell carcinoma

Squamous cell carcinoma originates from keratinocytes, which after the neoplastic transformation form irregular aggregates and grow uncontrollably [6]. Although SCC makes a smaller percentage of skin cancer cases than BCC, it has a higher tendency to become malignant [7]. Currently available methods of therapy for advanced SCC are characterized by low efficiency and have little effect on the overall survival [2].

One of the specific changes associated with SCC is mutation of the epidermal growth factor receptor (EGFR) gene. The contribution of this gene to the regulation of epithelial, stem and neuronal cell proliferation as well as survival is extremely important [1]. The signalling of EGFR in the proliferative part of the epithelium is to maintain control over the self-renewal of keratinocytes and inhibit differentiation [8]. Binding of the ligand leads to a change in the conformation of EGFR and then to di-

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merization with another EGFR or HER receptor. This reaction results in activation and phosphorylation associated with multiple signal transduction pathways. EGFR has been shown to be strongly expressed in metastatic SCC and is associated with a worse prognosis [1]. Uribe *et al.* detected EGFR overexpression in 73% of SCC cases with well-differentiated cells compared to normal epidermis [9]. Currently, two types of high-efficiency EGFR inhibitors are used – monoclonal antibodies that inhibit the formation of ligands and inhibitors of tyrosine kinase activity.

The risk of SCC occurrence is often associated with immunosuppressive treatment; patients undergoing immunosuppression are confirmed to have a higher disease risk and mutation burden [10, 11]. Tumours with a high tendency to mutate secrete immunogenic tumour neoantigens more often, which attracts effector T cells. It is possible to unleash them by blocking the programmed death-1 (PD-1) immune checkpoint [12]. By using PD-1 antibody, it reverses the PD-1-dependent attenuation of signalling through receptors of T-cells obtained by genetic engineering and amplifies antitumor response of primary lymphocytes [13].

Monoclonal antibodies

Cetuximab, a recombinant chimeric antibody, blocks the extracellular domain of the EGFR receptor. In 2006, it was approved by the FDA for the treatment of patients with advanced head and neck squamous cell carcinoma (HNSCC), in which cisplatin or radiotherapy was ineffective [1].

Maubec *et al.* evaluated the effect of cetuximab in a study which confirmed the effectiveness of this monoclonal antibody (Table 1) [14]. Unfortunately, many patients

Table 1. Selected studies using new advanced SCC therapies [14, 18–24]

Drug	Phase of clinical trial, number of patients	Dose	Outcome	Reference
Anti-EGFR:				
Cetuximab	Phase II 36 patients	400 mg/m^2 – 1st week 250 mg/m^2 weekly	General DCR – 69% RR – 28% PR = 8 CR = 2	[14]
Gefitinib	Phase II 47 patients	500 mg daily	RR – 10.7% DCR – 53%	[17]
	Phase II 18 patients	250 mg daily	SD – 27%	[18]
	Phase II 22 patients	250 mg daily	RR – 45.5% PR – 27.3% CR – 18.2%	[19]
	Phase II 37 patients	250 mg daily	SD = 14 PR = 4 PD = 19	[20] NCT00054691
	Phase II 22 patients	250 mg daily	Early stage of progression – 31.8%	
Erlotinib	Phase I 15 patients	150 mg daily (2 weeks before resection)	Disease-free survival: 60% No relapse 73% (n = 2)	[21]
	Phase II 39 patients	150 mg daily	Overall RR – 10% DCR – 72%	[22]
Immunotherapy:				
Cemiplimab	Phase I 26 patients	3 mg per 3 kg of body weight every 2 weeks	CR = 0 PR = 13 SD = 6 PD = 3	[24]
	Phase II 57 patients	3 mg per 3 kg of body weight every 2 weeks	CR = 4 PR = 24 SD = 9 PD = 11	

EGFR – epidermal growth factor receptor, DCR – disease control rate, RR – response rate, PR – partial response, CR – complete response, SD – stable disease, PD – progressive disease.

develop resistance to this targeted therapy. The exact mechanisms responsible for aforementioned resistance are not known. It is suggested that the FcγRIIIa polymorphism may affect the results of monoclonal antibody treatment [15]. The currently conducted study is aimed to check the correlation between the occurrence of those specific polymorphisms and progression-free survival [16].

Tyrosine kinase inhibitors

Gefitinib is an EGFR inhibitor: it inhibits autophosphorylation and receptor activation by attaching to an ATP binding site. Studies have shown that it decreases the growth of cell lines with detectable levels of EGFR and high levels of HER-2 [1]. It is a drug approved by the FDA for the treatment of non-small cell lung cancer [17]. Gefitinib studies have shown its capabilities to increase the level of disease control and level of response to treatment in advanced SCC, especially in adjuvant therapy (Table 1) [18–20]. However, the toxicity of aforementioned inhibitor suggests only partial efficacy of EGF receptor targeted therapy [20]. Therefore, studies determining safety and utility of gefitinib alone and in adjuvant therapy are still conducted (Table 2) [16].

Erlotinib, a quinazoline derivative, is a reversible ATP competitive inhibitor that impedes the cell cycle. It is used in the treatment of non-small cell lung cancer and advanced pancreatic cancer [1]. This inhibitor is potentially useful in adjuvant treatment, the toxicity profile appeared to be acceptable in comparison with control [21]. However, even though the monotherapy with erlotinib is feasible, it seems to give modest response [22]. Trials were completed to determine the ability of erlotinib to stop tumour growth by blocking the enzymes necessary for cell growth, but the results are yet to be published [16].

Targeted therapy, even though feasible, seems to show little to no positive results. Adverse events and partial efficacy associated with aforementioned treatment as well as possibility of resistance to EGFR inhibitors suggest further need of targeted therapy research.

Immunotherapy

Cemiplimab is a human, anti-PD-1 IgG4 stabilized anti-PD-1 antibody that blocks its interaction with PD-L1 and PD-L2. Thus, it reverses the PD-1-dependent attenuation of signalling by T-cell receptors on the T-lymphocytes obtained by genetic engineering and strengthens the antitumor response of primary lymphocytes [13]. Migden *et al.* pursued a clinical trial of cemiplimab therapeutic effect (Table 1). Approximately half of the examined patients showed response to immunotherapy. Moreover, at least 15% of the patients experienced adverse events [23].

Table 2. Ongoing clinical trials for advanced SCC therapy [16]

NCT number	Drug	Number of patients, admission criteria	Aim of the study	Status (results)
Cetuximab:				
NCT01133665	Cetuximab + lenalidomide	42 patients recurrent/metastatic SCC	Disease-free survival	Completed (median of survival 1.8)
Gefitinib:				
NCT00126555	Gefitinib	23 patients, recurrent/locally advanced SCC	Early progression rate	Completed (4 – complete response, 6 – partial response, 5 – stable disease)
NCT00054691	Gefitinib	40 patients, recurrent/metastatic SCC	Objective response	Completed (14 – stable disease, 4 – partial response, 19 – progressive disease)
Erlotinib:				
NCT00281866	Erlotinib hydrochloride	37 patients locally advanced/metastatic SCC, incurable through surgery and radiotherapy	Degree of response to therapy and the number of CA repetitions in intron 1 of EGFR	Completed, no results
Pembrolizumab:				
NCT02964559	Pembrolizumab	29 patients locally advanced/recurrent SCC incurable through surgery and radiotherapy	General response rate	Recruiting
NCT02883556	Pembrolizumab	39 patients locally advanced/recurrent SCC incurable through surgery, confirmed progression, PD-L1 + or PD-L1- disease	Response rate after 15 weeks	Active Not recruiting
NCT03452137	Atezolizumab	400 patients locally advanced SCC of head and neck	Event-free survival	Recruiting

SCC – squamous cell carcinoma, EGFR – epidermal growth factor receptor.

Another human anti-PD-L1 antibody is pembrolizumab. Currently, there are two studies assessing the effectiveness of this drug in advanced SCC therapy (Table 2). A phase III clinical trial is currently being conducted to evaluate atezolizumab in locally advanced SCC (Table 2) [16].

Basal cell carcinoma

Basal cell carcinoma accounts for 70–80% of all NMSCs, which makes it the most common skin cancer usually characterized by a milder course than SCC [24]. It is difficult to identify the source cells of BCC; Marzuka *et al.* did research indicating that BCC originates from keratinocytes or from hair follicle cells depending on the circumstances [25]. Even though BCC is considered a low risk carcinoma, some cases cannot be cured with traditional techniques. These locally advanced BCCs account for only 1–10% of all cases, and in about 0.003–0.5% of cancers distant metastases develop [24]. Typically, in BCC the overexpression of the Sonic Hedgehog signalling pathway occurs. This signalling pathway plays a very important role in the regulation of genes involved in cell maturation and proliferation [1]. Binding of the Hedgehog ligand to PATCHED (PTCH1), which is a transmembrane protein, prevents the binding of the 7TM Smoothened (SMO) receptor. Signal transduction triggered by SMO leads to the activation and nuclear localization of GLI transcription factors and ultimately, to the induction of target genes. 80–90% of mutations in BCC are mutations in the loss of PTCH1 function, approximately 10% are SMO activating mutations leading to constitutive path activation [26]. The level of the GLI1 transcription factor, which plays an important role in the signalling pathway, is elevated in tumour tissues, which confirms its participation in the development of BCC [1].

Vismodegib, the first SMO antagonist

Vismodegib is the first inhibitor of the Hedgehog pathway. It was approved by the FDA in 2012 for the treatment of advanced BCC and Gorlin syndrome [1]. This antagonist binds to SMO, thereby blocking further activation of the signalling pathway. This results in the suppression of Gli1/2 transcriptional activity, and thus causes BCC suppression [27]. Sekulic *et al.* presented a new therapeutic option for patients with advanced BCC and led to the approval of the drug by the FDA (Table 3) [28].

In 2014, a multicentre phase II trial confirmed vismodegib treatment as a drug with long-lasting effects, especially for locally advanced BCC (Table 3) [29]. Despite many side effects of vismodegib in BCC therapy, patients can derive significant therapeutic benefits (Table 3) [30]. Thanks to data acquired by Chang *et al.*, it is suggested that patients who are suffering from a locally advanced disease respond better to therapy (Table 3) [31].

Currently, two studies are being conducted with vismodegib in combination with radiotherapy (Table 4) [16].

Other Hedgehog pathway inhibitors

Sonidegib is an inhibitor of the Hedgehog signalling pathway, which targets the SMO protein. The drug seems to be a promising candidate for advanced BCC therapy, which cannot be cured by traditional methods [32].

A phase II trial was conducted to establish a safe and effective dose of sonidegib in the treatment of advanced BCC (Table 3). Based on objective response and adverse events, 200 mg showed better results in locally advanced cases and 800 mg in metastatic SCC [33]. Twelve months after the end of the study, Dummer *et al.* carried out a reanalysis of previously treated patients, where previous results were confirmed [34].

Danial *et al.* clinical trial suggests that patients who developed resistance to vismodegib treatment exhibited similar resistance to treatment with sonidegib [35]. A study was also conducted to assess the efficacy of sonidegib in patients previously treated with non-LDE225 SMO inhibitor (Table 4) [16]. The results obtained confirm the thesis presented by Danial *et al.*, namely the survival of patients refractory to treatment with SMO inhibitors is poor [35].

Another inhibitor of the Hedgehog pathway that has the potential to treat advanced BCC is itraconazole. The combination therapy of itraconazole and arsenic trioxide seems to be an appropriate treatment for patients with advanced BCC, however, the results obtained indicate the need for continuous intake of the drug (Table 3) [36].

A study to assess the effectiveness of the combined therapy on the level of Gli1 expression is also planned (Table 4) [16].

Immunotherapy

Since BCC is characterized by a low risk of neoplasia, there are no studies on the effectiveness and safety of immunotherapeutic drugs yet. But in the light of the information that many patients develop resistance to inhibitors of the Hedgehog pathway it might be an alternative treatment to targeted therapy. The promising prospect is the use of cemiplimab for patients who demonstrated resistance to Hedgehog pathway inhibitors. In the near future a monotherapy study will be performed on patients with advanced BCC. A clinical trial on the use of nivolumab alone or plus ipilimumab is currently recruiting (Table 4) [16].

Melanoma

Melanoma is one of the most aggressive skin cancers with the highest mortality rate. It arises from cells after neoplastic transformation to pagenoid, spindle-like, small and epithelioid melanocytes also containing melanin granules [37].

The increase in the incidence in the Caucasian population made it the most common cancer among people

Table 3. Selected studies using new advanced BCC therapies [28–31, 33–36]

Drug	Phase of clinical trial, number of patients	Dose	Outcome	Reference
Hedgehog pathway inhibitors:				
Vismodegib	Phase II 33 patients	150 mg daily	General response level Metastatic BCC – 30% Locally advanced BCC – 43%, including CR – 21% 7 deaths	[28]
	Phase II 104 patients,	150 mg daily	General response level Metastatic BCC – 15% CR = 0 PR = 15 PD = 2 SD = 15 General response level Locally advanced BCC – 38% CR = 20 PR =18 PD = 6 SD = 15	[29]
	Phase II, after 24 months: 96 patients	150 mg daily	After 24 months General response level Metastatic BCC – 16% CR = 0 PR = 16 PD = 2 SD = 14 General response level Locally advanced BCC – 38% CR = 20 PR = 18 PD = 6 SD = 15	
	Open clinical trial 499 patients	150 mg daily in 28 days' cycles	Locally advanced BCC (*n* = 453) General response = 302 CR = 153 PR = 149 Metastatic BCC (*n* = 29) General response = 11 CR = 2 PR = 9	[30]
	Open clinical trial 119 patients	150 mg daily	Objective response level Locally advanced BCC – 46.4% Metastatic BCC – 30.8%	[31]
Sonidegib	Phase II 230 patients	200 mg daily 800 mg daily	Objective response level 200 mg – 41.0% 800 mg – 32.5% Locally advanced BCC 200 mg – 47.0% 800 mg – 35.2% Metastatic BCC 200 mg – 15.4% 800 mg – 17.4%	[33]
	Phase II 230 patients	200 mg daily 800 mg daily	Objective response level Locally advanced BCC 200 mg – 57.6% 800 mg – 43.8% Metastatic BCC 200 mg – 7.7% 800 mg – 17.4%	[34]
	Open clinical trial 9 patients	800 mg daily w in 28 day cycles	PD = 5 SD = 3 Treatment was discontinued evaluation is not possible (n = 1)	[35]
	Open clinical trial 11 patients	800 mg daily	Progression-free survival: SMO-resistant patients – 6 weeks Patients who developed SMO resistance during treatment – 36 weeks	[35] NCT01529450
Itraconazole + nitrous oxide	Phase II 5 patients	0.3 mg/kg nitrous oxide daily for 5 days every 28 days, 400 mg itraconazole daily	General, reduced level of Gli1 relay by 75% SD = 3	[36]

RR – response rate, PR – partial response, CR – complete response, PD – progressive disease, SD – stable disease.

with a fair skin type. The statistical analysis showed an increase in mortality as a result of advanced disease between 1977 and 1990, while in 1990–2002 there was a slight downward trend [37]. Among the mutations identified in patients suffering from cutaneous melanoma, a large percentage constitutes disturbances of the PI3K/PTEN/Akt/mTOR and Raf/MEK/ERK signalling pathways. Mutation in the NRAS gene leads to the constitutive ac-

Table 4. Ongoing clinical trials for advanced BCC therapy [16]

NCT number	Drug	Number of patients, admission criteria	Aim of the study	Status (results)
Vismodegib:				
NCT02674009	Vismodegib	55 patients locally advanced BCC incurable by surgical and radiotherapeutic methods	Time to respond to treatment	Active not recruiting
NCT02371967	Vismodegib	40 patients BCC meeting the previously agreed cohort requirements	Objective response level, time of response, duration of response, non-relapsing survival, overall survival objective degree of response, time of response, duration of response, relapse-free survival, overall survival	Active, not recruiting
NCT01835626	Vismodegib + radiotherapy	24 patients locally advanced BCC, inoperable, without contraindications for radiotherapy, radiotherapy allowed, provided that the disease relapses	Local control after the end of therapy	Recruiting
NCT02956889	Vismodegib + radiotherapy	42 patients inoperable BCC, previous radiotherapy with another BCC	Assessment of the activity of the studied therapy by the proportion of patients free from progression	Recruiting
Itraconazole:				
NCT02699723	Itraconazole + arsenic trioxide	5 patients BCC incurable by standard treatment or SMO antagonists like vismodegib	Gli1 level	Not recruiting
Cemiplimab:				
NCT03132636	Cemiplimab	137 patients invasive BCC, progression of the disease during treatment with Hedgehog pathway inhibitors or resistance to this therapy	General response level to monotherapy	Not recruiting
NCT03521830	Nivolumab + ipilimumab	40 patients locally advanced unresectable/ metastatic BCC	Objective response rate	Recruiting

tivation of the signalling pathway involving RAF serine-threonine kinases and results in an increased proliferation of melanocytes [38].

Recently, novel therapeutic options have emerged thanks to the approval of six new chemotherapeutics in the EU, USA and Japan. Ipilimumab, nivolumab and pembrolizumab (immunotherapy) and vemurafenib, dabrafenib and trametinib (targeted therapy) have significantly expanded the outlook for melanoma treatment.

BRAF inhibitors

In approximately 40–50% of melanoma cases, the mutation in the BRAF oncogene is activated, and 90% of them are found in codon 600, where valine is replaced by glutamic acid (V600E) or lysine (V600K). This type of melanoma increases the probability of obtaining positive results of targeted therapy. It is worth noting that the wild-type BRAF status is likely to activate the MAPK pathway [39].

Vemurafenib is a potent, selective inhibitor that binds to the mutant BRAF proteins. McArthut *et al*. evaluated the efficacy of vemurafenib in the treatment of advanced melanoma (BRAD V600E and V600K) compared to dacarbazine [40]. The positive response was significantly higher in the vemurafenib group (Table 5). Queirolo *et al*. suggested combined therapy with fotemustine for BRAF-refractory patients [41]. However, there are still no results confirming the long-term efficacy.

Dabrafenib is a drug that in 2013 was approved by the FDA for the treatment of advanced melanoma with the BRAF V600 mutation. It significantly improves the survival of participants without disease progression compared to dacarbazine and has long-term efficacy (Table 5). However, the results are difficult to estimate, many patients who showed the progression during dacarbazine treatment were transferred to the BRAF inhibitor group [41–43].

LGX818 is a selective inhibitor of BRAF, its half-life is 10 times longer than for other BRAF inhibitors. Dum-

Table 5. Selected studies using new advanced melanoma therapies [40–48, 50, 51]

Drug	Phase of clinical trial, number of patients	Dose	Outcome	Reference
BRAF inhibitors:				
Vemurafenib or dacarbazine	Phase III 675 patients	Vemurafenib: 960 mg twice a day Dacarbazine: 100 mg/m^2 every 3 weeks	Median OS: Vemurafenib – 13.6 months Dacarbazine – 9.7 months BRAF (V600E) Vemurafenib – 13.3 months Dacarbazine – 10.0 months BRAF (V600K) Vemurafenib – 14.6 months Dacarbazine – 7.6 months Median PFS: Vemurafenib – 6.9 months Dacarbazine – 1.6 months BRAF (V600E) Vemurafenib – 6.9 months Dacarbazine – 1.6 months BRAF (V600K) Vemurafenib – 5.9 months Dacarbazine – 1.7 months	[40]
Vemurafenib + fotemustine	Phase II 31 patients	Vemurafenib: 960 mg twice a day Fotemustine: 100 mg/m^2 intravenously every 3 weeks	Median PFS – 3.9 months CR – 1 PR – 4 SD – 14 Median OS: 5.8 months (from enrolment) 15.4 months (from previous vemurafenib treatment)	[41]
Dabrafenib or dacarbazine	Phase III 250 patients	Dabrafenib: 150 mg twice a day Dacarbazine: 100 mg/m^2 every 3 weeks	Median PFS: Dabrafenib – 5.1 months Dacarbazine – 2.7 months	[42]
			Median OS: Dabrafenib – 20.0 months Dacarbazine – 15.6 months	[43]
LGX818	Phase I 54 patients	50–700 mg daily or 75–150 mg twice a day	450 mg – tolerated dose Non-treated patients PR – 67% Treated patients PR – 8.3%	[44]
MEK inhibitors:				
Trametinib, dacarbazine, paclitaxel	Phase III 322 patients	Trametinib: 2 mg daily Dacarbazine: 100 mg/m^2 every 3 weeks Paclitaksel: 175 mg/m^2 every 3 weeks	Median PFS: Trametinib – 4.8 months Chemotherapy – 1.5 months At 6 months of therapy: OS: Trametinib – 81% Chemotherapy – 67%	[45]
Binimetinib or dacarbazine	Phase III 402 patients	Binimetinib: 45 mg daily Dacarbazine: 1000 mg/m^2 every 3 weeks	Median PFS: Binimetinib – 2.8 months dacarbazine – 15 months	[46]
Combined therapy MEK/BRAF:				
Dabrafenib + trametinib or vemurafenib	Phase III 704 patients	Dabrafenib + trametinib: 150 mg twice a day + 2 mg daily or Vemurafenib 960 mg twice a day	OS in 12 month of therapy: Dabrafenib + trametinib – 72% Vemurafenib – 65% Median PFS: Dabrafenib + trametinib – 11.4 months Vemurafenib – 7.3 months overall RR Dabrafenib + trametinib – 64% Vemurafenib – 51%	[47]

Table 5. Cont.

Drug	Phase of clinical trial, number of patients	Dose	Outcome	Reference
LGX818 + binimetinib	Phase Ib/II 30 patients	LGX818 + binimetinib: 50 mg + 45mg 100 mg + 45mg 200 mg + 45mg 400 mg + 45mg 450 mg + 45mg 600 mg + 45mg	Recommended doses: 450 mg + 45 mg 600 mg + 45 mg CR – 11% of patients not treated with BRAF inhibitors PR – 78% of patients not treated with BRAF inhibitors PR – 21% of patients treated with BRAF inhibitors	[48]
Inhibitors of immune checkpoints:				
Ipilimumab	Collective analysis 1,861 patients 2,984 patients	3 mg/kg or 10 mg/kg	*N* = 1.861 Median OS – 11.4 months 3-year survival: General – 22% Patients not treated before – 26% Patients treated before – 20% *N* = 2,985 Median OS – 9.5 months	[50]
	Phase II 21 patients	Ipilimumab: 10 mg/kg + dacarbazine, 850 mg/m^2	Survival after a year of therapy – 66.7%	[16] NCT01681212
Nivolumab or chemotherapy	Phase III 321 patients	Nivolumab: 3 mg/kg every 2 weeks	Nivolumab Overall response = 38 Chemotherapy Overall response = 5	[51]
Pembrolizumab or ipilimumab	Phase III 834 patients	Pembrolizumab: 10 mg/kg every 2/3 weeks or Ipilimumab: 3 mg/kg every 3 weeks	12-month SR: Pembrolizumab 2 w. – 74.1% Pembrolizumab 3 w. – 68.4% Ipilimumab – 58.2% RR: Pembrolizumab 2 w. – 33.7% Pembrolizumab 3 w. – 33.9% Ipilimumab – 11.9%	[52]

OS – overall survival, PFS – progression-free survival, PR – partial response, CR – complete response, SD – stable disease, SR – survival rate, RR – response rate.

mer *et al.* presented the effectiveness of this drug in the therapy of advanced melanoma (BRAF V600) [44]. They also determined the most effective dose, 450 mg daily. Currently, a study is carried out to confirm this analysis (Table 6) [16].

MEK inhibitors

BRAF phosphorylates and activates MEK proteins that have the ability to activate ERK, which leads to an increased proliferation of tumour cells [44]. One of the MEK1/2 inhibitors is trametinib, which is characterized by high selectivity and can lead to tumour regression. Personalized therapy with trametinib is significantly more efficient than chemotherapy (Table 5) [45]. The effectiveness of this inhibitor in not-BRAF V600 mutated melanoma is being measured (Table 6) [16].

More information on the beneficial effects of MEK inhibitor has been provided by binimetinib studies. Dummer *et al*. analysed its effect on advanced melanoma with the mutation of the NRAS gene. The median progression-free survival in patients with NRAS indicates the therapeutic potential of binimetinib (Table 5) [46].

MEK and BRAF inhibitors combination

The effectiveness of BRAF and MEK inhibitors prompted researchers to analyse the possibility of combination therapy. Combined therapy has been shown to significantly improve the effectiveness of treatment compared to monotherapy (Table 5). It is also worth noting that the combination of dabrafenib and trametinib did not cause any increase in toxicity [47].

The effectiveness of combining LGX818 with binimetinib was also examined (Table 5). It has been shown that the use of these inhibitors in the treatment of melanoma (BRAF V600) is safe [48].

Immunotherapy

Ipilimumab was approved in 2011, which significantly contributed to the development of advanced melanoma treatment. The aforementioned antibody is directed

Table 6. Ongoing clinical trials for advanced melanoma therapy [16]

NCT number	Drug	Number of patients, admission criteria	Aim of the study	Status (results)
LGX818:				
NCT01436656	LGX818	107 patients locally advanced or metastatic melanoma with the BRAF V600 mutation	Occurrence of dose-limiting toxicity	Active Not recruiting
Trametinib:				
NCT02296112	Trametinib	9 patients advanced melanoma with a mutation other than BRAF V600	General response rate in the "high affinity" group	Active Not recruiting
Pembrolizumab:				
NCT02818023	Vemurafenib + pembrolizumab + cobimetinib	50 patients inoperable melanoma III or IV with BRAF V600E or V600K mutations	Percentage of subjects experiencing dose-limiting toxicity, overall response rate	Recruiting
NCT02858921	Dabrafenib + trametinib, next pembrolizumab or Dabrafenib + trametinib + pembrolizumab or Pembrolizumab	60 patients inoperable melanoma with the BRAF V600 mutation	Response rate	Recruiting

against CTLA-4 and by blocking it, it increases T-cell proliferation. Activated T-lymphocytes infiltrate the tumour leading to the death of cancer cells [49]. Examination of 2985 patients confirmed the long-term effectiveness of ipilimumab in the treatment of melanoma [50].

Nivolumab and pembrolizumab are monoclonal antibodies blocking PD-1, thus stimulating the body's immune response to fight cancer. Both of these drugs were approved by the FDA in 2014 for the treatment of advanced melanoma. Treatment with nivolumab brings therapeutic benefits to a larger number of people than chemotherapy and is associated with fewer side effects (Table 6) [51].

Robert *et al.* compared pembrolizumab and ipilimumab. All the results obtained showed that pembrolizumab prolonged progression-free survival and overall survival (Table 5). It is also worth mentioning that it caused fewer dangerous side effects [51].

Combination therapy: immunotherapy and targeted therapy

Thanks to the effectiveness of targeted therapy and immunotherapy, research combining the two methods is currently carried out. One of the studies (phase I) uses vemurafenib and pembrolizumab. Patients with inoperable melanoma (BRAF V600) will be analysed for the appropriate dose and general response (Table 6) [16].

Another study uses pembrolizumab in combination with trametinib and dabrafenib. It is planned to divide patients into three groups receiving (1) dabrafenib and trametinib, (2) dabrafenib, trametinib and pembrolizumab, (3) exclusively pembrolizumab (Table 6) [16].

Conclusions

Skin cancers present a serious clinical problem. The issue of treating these cancers is extremely important as every year the percentage of people diagnosed increases, and traditional therapeutic methods prove to be insufficient.

There are not many studies on advanced SCC treatment, but those published recently focused on targeting the EGFR receptor. The problem to be faced in the future is the patients' development of resistance to EGFR inhibitors. The available data suggest high efficacy of treatment with anti-PD-1 antibodies for highly mutated cancers, yet it still needs further research.

Targeted therapy is the main focus of interest in the treatment of advanced BCC. Inhibitors of the Hedgehog pathway have proven efficacy and long-term activity. The possibility of patients developing resistance to therapy is the main remaining problem, which can be dealt with in the future by application of immunotherapy.

The FDA approval of immunotherapeutic drugs and targeted therapy has contributed to a significant improvement in therapeutic options for patients with cutaneous melanoma. The range of currently available BRAF kinase inhibitors and MEK inhibitors was widened.

Currently conducted studies focus mainly on immunotherapy or combined therapy.

It seems important that subsequent clinical trials should be based on the analysis of the effectiveness of combination therapies, combining drugs commonly used in monotherapy, in order to obtain the best possible results.

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Conflict of interest

The authors declare no conflict of interest.

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