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-
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 neo-antigens 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

| Drug      | Phase of clinical trial, number of patients | Dose                          | Outcome                      | Reference |
|-----------|--------------------------------------------|-------------------------------|------------------------------|-----------|
| Anti-EGFR:| Cetuximab                                   | Phase II 36 patients          | 400 mg/m² – 1st week 250 mg/m² weekly | General DCR – 69% RR – 28% 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 Fc\(\gamma\)RIIIa 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                               |
| NCT02888556        | 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 that 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 re-analysis 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...
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 activa-

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                  |                               |           |
|                           | Phase II 104 patients                       | 150 mg daily              | General response level         |           |
|                           |                                             | Metastatic BCC – 15%      |                               |           |
|                           |                                             | CR = 0                    |                               |           |
|                           |                                             | PR = 15                   |                               |           |
|                           |                                             | PD = 2                    |                               |           |
|                           |                                             | SD = 15                   |                               |           |
|                           | Phase II after 24 months 96 patients        | 150 mg daily              | General response level         |           |
|                           |                                             | Metastatic BCC – 16%      |                               |           |
|                           |                                             | CR = 0                    |                               |           |
|                           |                                             | PR = 16                   |                               |           |
|                           |                                             | PD = 2                    |                               |           |
|                           |                                             | SD = 14                   |                               |           |
|                           | Open clinical trial 499 patients            | 150 mg daily              | Locally advanced BCC – 38%     |           |
|                           |                                             | CR = 20                   |                               |           |
|                           |                                             | PR = 18                   |                               |           |
|                           |                                             | PD = 6                    |                               |           |
|                           |                                             | SD = 15                   |                               |           |
| 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] |
|                           |                                             | Metastatic BCC – 30.8%    |                               |           |
| Sonidegib                 | Phase II 230 patients                       | 200 mg daily              | Objective response level       |           |
|                           |                                             | 800 mg daily              | Metastatic BCC – 30.8%         |           |
|                           |                                             | Locally advanced BCC      |                               |           |
|                           |                                             | 200 mg – 41.0%            |                               |           |
|                           |                                             | 800 mg – 32.5%            |                               |           |
|                           | Phase II 230 patients                       | 200 mg daily              | Objective response level       |           |
|                           |                                             | 800 mg daily              | Metastatic BCC – 30.8%         |           |
|                           |                                             | Locally advanced BCC      |                               |           |
|                           |                                             | 200 mg – 47.0%            |                               |           |
|                           |                                             | 800 mg – 35.2%            |                               |           |
|                           | Open clinical trial 9 patients              | 800 mg daily              | Objective response level       |           |
|                           |                                             | w in 28 day cycles        | Metastatic BCC – 30.8%         |           |
|                           |                                             | Locally advanced BCC      |                               |           |
|                           |                                             | 200 mg – 57.6%            |                               |           |
|                           |                                             | 800 mg – 43.8%            |                               |           |
|                           |                                             | Metastatic BCC             |                               |           |
|                           |                                             | 200 mg – 7.7%             |                               |           |
|                           |                                             | 800 mg – 14.7%            |                               |           |
| Treatment was discontinued evaluation is not possible (n = 1) |
| 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] |

RR – response rate, PR – partial response, CR – complete response, PD – progressive disease, SD – stable disease.
Novel therapies for advanced skin carcinomas

Recent advances in dermatology and allergology have introduced new therapeutic options for advanced skin carcinomas. These include targeted and immunotherapies, which have significantly expanded the treatment options for patients with melanoma and basal cell carcinoma (BCC).

**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. McArthur 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.

**Targeted therapy**

BRAF inhibitors are effective in BRAF V600 mutated melanomas and BCC. 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].

**Immunotherapy**

Ipilimumab, nivolumab, and pembrolizumab are effective in BRAF wild-type melanoma. Queirolo et al. suggested combined therapy with fotemustine for BRAF-refractory patients [41]. However, there are still no results confirming the long-term efficacy.

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

| NCT number       | Drug                           | Number of patients, admission criteria                                      | Aim of the study                                                                 | Status (results)          |
|------------------|--------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------|
| NCT02674009      | Vismodegib                     | 55 patients locally advanced BCC incurable by surgical and radiotherapeutic    | 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 | 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                |
| NCT02699723      | Itraconazole + arsenic trioxide | 5 patients BCC incurable by standard treatment or SMO antagonists like vismodegib | GlI1 level                                                                      | Not recruiting            |
| 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                |

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LGX818 is a selective inhibitor of BRAF, its half-life is 10 times longer than for other BRAF inhibitors. Dumb-
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/m² 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 – 5.9 months  
Dacarbazine – 1.7 months | [40] |
| | | | 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] |
| Vemurafenib + fotemustine | Phase II 31 patients | Vemurafenib: 960 mg twice a day  
Fotemustine: 100 mg/m² intravenously every 3 weeks | Median PFS:  
Dabrafenib – 5.1 months  
Dacarbazine – 2.7 months | [42] |
| Dabrafenib or dacarbazine | Phase III 250 patients | Dabrafenib: 150 mg twice a day  
Dacarbazine: 100 mg/m² every 3 weeks | Median PFS:  
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/m² every 3 weeks  
Paclitaxel: 175 mg/m² 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/m² 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  
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] |
Novel therapies for advanced skin carcinomas

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

| Drug                          | Phase of clinical trial, number of patients | Dose                     | Outcome                          | Reference |
|-------------------------------|--------------------------------------------|--------------------------|----------------------------------|-----------|
| LGX818 + binimetinib          | Phase Ib/II 30 patients                    | LGX818 + binimetinib:    | Recommended doses:               | [48]      |
|                               |                                            | 50 mg + 45mg             | 450 mg + 45 mg                   |           |
|                               |                                            | 100 mg + 45mg            | 600 mg + 45 mg                   |           |
|                               |                                            | 200 mg + 45mg            | CR – 11% of patients not treated |           |
|                               |                                            | 400 mg + 45mg            | with BRAF inhibitors             |           |
|                               |                                            | 450 mg + 45mg            | PR – 78% of patients not treated |           |
|                               |                                            | 600 mg + 45mg            | with BRAF inhibitors             |           |
|                               |                                            |                          | PR – 21% of patients treated     |           |
|                               |                                            |                          | with BRAF inhibitors             |           |

Inhibitors of immune checkpoints:

| Drug                          | Phase of clinical trial, number of patients | Dose                     | Outcome                          | Reference |
|-------------------------------|--------------------------------------------|--------------------------|----------------------------------|-----------|
| Ipilimumab                    | Collective analysis 1,861 patients          | 3 mg/kg or 10 mg/kg      | N = 1.861                        | [50]      |
|                               |                                            |                          | 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           |           |
| Nivolumab or chemotherapy     | Phase II 21 patients                       | Nivolumab: 10 mg/kg +   | Survival after a year of therapy | [16]      |
|                               |                                            | dacarbazine, 850 mg/m²   | ~ 66.7%                          | NCT01681212|
| Pembrolizumab or ipilimumab  | Phase III 321 patients                     | Nivolumab: 3 mg/kg every 2 weeks | Nivolumab Overall response = 38 | [51]      |
|                               |                                            |                          | Chemotherapy Overall response = 5|           |
|                               | Phase III 834 patients                     | Pembrolizumab: 10 mg/kg every 2/3 weeks | 12-month SR: Pembrolizumab 2 w. – 74.1% | [52]      |
|                               |                                            | or                     | Pembrolizumab 3 w. – 68.4%       |           |
|                               |                                            | Ipilimumab: 3 mg/kg every 3 weeks | Pembrolizumab – 58.2%            |           |
|                               |                                            |                          | Ipilimumab – 33.7%               |           |
|                               |                                            |                          | Pembrolizumab – 33.9%            |           |
|                               |                                            |                          | Ipilimumab – 11.9%               |           |

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

**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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