VIA MEDICA

CASE REPORT

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The use of vismodegib in the treatment of basal cell carcinoma based on case reports

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ABSTRACT

Basal cell carcinoma (BCC) is the most common skin cancer, usually located on the skin of the face and neck. Locally advanced cancer is diagnosed by about 5–10% of patients, while the metastatic disease is diagnosed in 0.0028 to 0.55% of cases. The primary treatment of locally advanced disease is radical surgery, and in non-operative cases — radiotherapy. For patients not eligible for local therapy and those with metastatic disease, systemic therapies, including hedgehog inhibitor — vismodegib — is used. In the Department of Melanoma and Soft Tissue and Bone Sarcomas, Maria Sklodowska-Curie Institute — Oncology Center several patients with BCC, not eligible for local therapy, are currently systemically treated. Vismodegib is registered for the use in adults with symptomatic metastatic basal cell carcinoma or locally advanced basal cell carcinoma that does not meet the criteria for surgical treatment or radiotherapy. In this paper, we present and discuss a case of BCC cancer in a metastatic setting and a case of a patient being treated for locally advanced disease not eligible for surgery and radiotherapy. The cases presented here confirm that vismodegib treatment, currently available in the national drug access program, provides an objective response, improvement in quality of life, and probably extension of survival.
Key words: basal cell carcinoma, hedgehog pathway, vismodegib

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Introduction

Basal cell carcinoma (BCC) is the most common skin cancer and the most common cancer in humans. The incidence of skin cancer increases primarily due to increased exposure to ultraviolet radiation. The average risk of BCC for Caucasians is between 5 and 30%. In 80% of cases the tumour develops in the skin of the face and neck, in 15% in the trunk and 5% in the trunk and limbs. The main BCC treatment modality is curative surgery, and in non-operative cases radiotherapy is the effective method. Locally advanced cancer is diagnosed in about 5–10% of patients, while the metastatic disease is diagnosed in the range of 0.0028–0.55%. In metastatic disease cases, the median overall survival is approximately 8–14 months. The systemic therapy, including hedgehog inhibitor, vismodegib, is used in the treatment of patients not eligible for radiotherapy and/or surgical treatment [1, 3, 15].

Currently, in the Department of Melanoma and Soft Tissue and Bone Sarcomas (KNTMKiCz), several basal cell carcinoma patients are being treated with vismodegib. The remaining therapeutic options have already been exhausted for these patients. Treatment is conducted as part of the National Health Fund (NHF) drug access program, which was launched in January 2017 [2].

Enrolment of patients in the drug access program is carried out by the Coordination Team for the Treatment of Basal Cell Skin Cancer, appointed by the President of the National Health Fund. Only patients with histologically confirmed locally advanced BCC or symptomatic BCC with distant metastases are eligible for the drug access. The treatment may be applied to patients with inoperable tumours, those who have contraindications

for surgical treatment, who have progressed after radiotherapy, or have contraindications for radiotherapy. Contraindications to surgical treatment are defined as a recurrence of BCC in the same location after surgery and a small probability of cure after another resection or predicted risk of significant disability and/or deformation after a plausible surgery or other contraindications for surgical treatment such as removal of part of the facial skeleton, for example nose, ear, eyelid, or eyeball; or need to amputate the limb for tumour resection. In the case of metastatic disease, the enrolment criteria for the treatment with vismodegib include histopathological confirmation of BCC in distant metastases. Patients with other cancers are excluded. The access program is dedicated for adult patients. The condition for vismodegib treatment in patients of childbearing potential is compliance with the current characteristics of the medicinal product requirements for the use of effective contraception. The drug is characterised by a very high embryotoxic and teratogenic potential, and its use is associated with the need to comply with the detailed program of effective pregnancy prevention described in product characteristics [1, 2].

Discussion of two cases of patients treated with vismodegib

BBC patient beyond surgery and radiotherapy possibilities

In November 2016 in the KNTMKiCz clinic, a 64-year-old woman with basal-cell skin cancer of the nose and left cheek with infiltration of orbital tissue and rush to the left and medial right eye (cT4N0M0) was consulted. The patient has been observing the infiltration within her face for about 10 years, and for two years this infiltration had gradually increased. The tomographic examination revealed "thickening and infiltration with the features of contrast-enhancement of the soft surface tissues around the nasal bridge and the lower part of the forehead affecting the eyelids, especially on the left side, involving the soft tissues of the nose and the buccal part of the cheek on the left side. The left bone of the nose was invisible, with features of destruction. Enlarged lymph nodes 19 mm around the angle of the mandible, along the neck vessels on both sides up to 20 mm, and under the sternocleidomastoid muscle up to 10 mm". Magnetic resonance imaging (MRI) revealed that "in the anteromedial part of the left eye socket a pathological mass is visible, passing from the soft tissues of the nose, involving the eyelid, infiltrating the periocular adipose tissue on the medial side, with the inclusion of the ocular attachment of the medial rectus muscle, and adhering to the anteromedial part of the left eyeball, partly to the anterior chamber; however, the continuity of the outer outline of eyeball seems to be preserved". The patient was consulted with an ophthalmologist and a neurosurgeon. Due to the large extent of potential surgery, the need to remove some orbital bone and ethmoid sinus, and the risk of cerebrospinal fluid leakage, as well as the risk of significant facial deformation resulting from the extent of the surgery and the high risk of non-radical surgery, by the decision of a multidisciplinary team the patient was disqualified from surgery. The patient had no significant concomitant diseases.

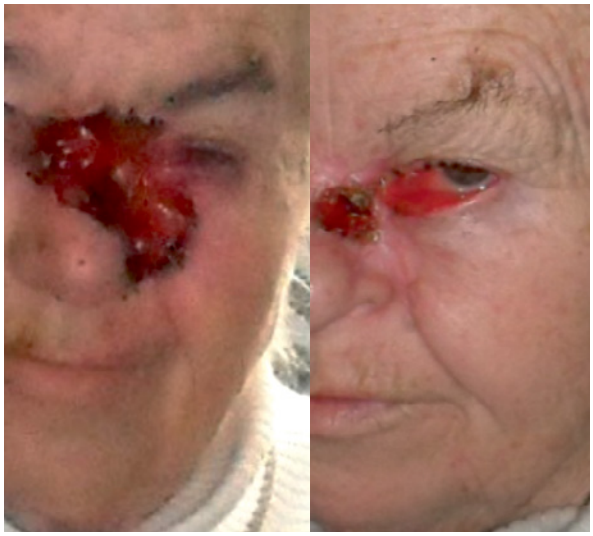

Figure 1. Pictures of the patient taken before starting treatment with vismodegib in December 2016 and during treatment in August 2017

In December 2016, the patient started treatment with vismodegib. The patient is regularly monitored at the KNTMKiCz clinic. The current tolerance of treatment is very good, no side effects of the treatment have been observed, and the patient takes medication regularly as recommended. During the treatment, gradual regression of lesions was observed (Fig. 1). The last follow-up visit took place on November 2, 2017. In the physical examination, except for the lesion in the face, no significant abnormalities were found, vismodegib was taken by the patient regularly without side effects, and a tendency to heal skin lesions was observed. In laboratory tests the patient had no significant abnormalities. In the next follow-up CT examination performed on November 7, 2017, the disease had stabilised: "compared to the previous scan from 08.2017, visible loss of the nasal bone and part of the nose on the left side, covering the medial region of the corner of the eye, thickening of the skin coating to 5 mm as before; no enlarged lymph nodes were found in the area covered by the scan" (Fig. 1).

The patient achieved partial remission with good tolerance of treatment.

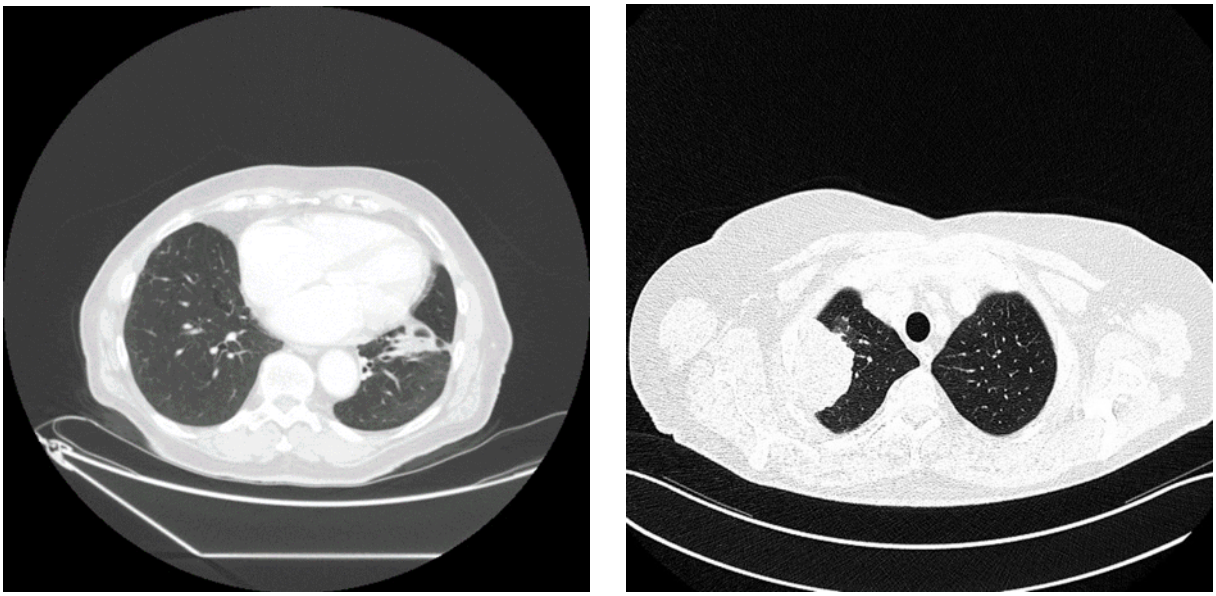

Figure 2. Lung metastases CT scan images of patient treated with vismodegib due to BCC, 02.06.2017 (description in the text)

The patient with metastatic BCC

The patient, aged 80 years, was referred to the KNTMKiCz due to BCC with lung metastases, without enlargement of the lymph nodes, detected accidentally during hospitalisation due to atrial fibrillation in the district hospital. During this hospitalisation, material for histopathological examination was collected, in which BCC metastasis was found. The patient had no respiratory symptoms, with arterial hypertension and atrial fibrillation in medical history. The patient had resection of a lesion on the skin of the frontal area in 2006. The patient did not receive the postoperative histopathological result. The histology slides from the skin tumour from the forehead resected in 2006 were consulted in the Pathology Department of COI, and the presence of basal cell carcinoma of the skin (carcinoma basocellulare) removed radically (large tumour 3.5 cm diameter) was found. Slides from a biopsy of lesions in the lung were also consulted at the Pathology Department of COI. "On the basis of the microscopic image, it cannot be unambiguously determined whether there are two independent cancers with morphologically similar stitching or with the metastasis of skin cancer to the lungs. According to the literature, a large primary skin lesion (3.5 cm), location within the head and/or neck (in this case skin cancer of the forehead) and multiple (at least two) pulmonary changes of the basaloid cancer indicate for the lung cancer metastasis — in this case, the metastasis of basal cell carcinoma of the skin to the lungs should be considered highly probable".

On 06.06.2017 the patient started treatment with vismodegib with a dose of 150 mg per day, orally. During the first month of treatment, general weakness and loss of appetite were observed, gradually decreasing during treatment. From the third treatment course there occurred periodically morning calf cramps, slight deterioration in appetite, G1 taste disturbances, and hair loss G1 according to CTCAE.

In a computed tomography (CT) scan of the chest from 02/06/2017 "on the border of seg. 8 and 9 of the left lung nodular change 55 × 48 × 53 mm, in the peripheral part of the upper lobe of the right lung tumour 70 × 41 × 66 mm, moreover moderate numerous mediastinal and right hilar lymph nodes, the largest with dimensions: right lower paratracheal 18 × 12 mm, 21 × 16 mm and in the right hilar 20 × 14 mm" were described (Fig. 2).

In the follow-up chest CT scan of August 29, 2017 "infiltration in the lower lobe of the left lung, currently located circumferentially with smaller dimensions (35 × 27 mm), infiltration in the upper lobe right peripherally presently smaller in size (35 × 21 mm), mediastinal lymph nodes up to 11 mm in the short axis — in comparative assessment, partial regression of lesions in chest" were described (Fig. 3).

In the follow-up CT scan of October 31, 2017 "the size of nodes and tumours in the chest as before — in the surround of nodular infiltration in the upper lobe of the right lung quite numerous nodular lesions up to 8 mm are visible, which may correspond to the obstructed bronchi — for further follow-up" (Fig. 4).

Discussion

Patients with locally advanced basal cell carcinoma, who are not eligible for surgery or radiotherapy, and pa-

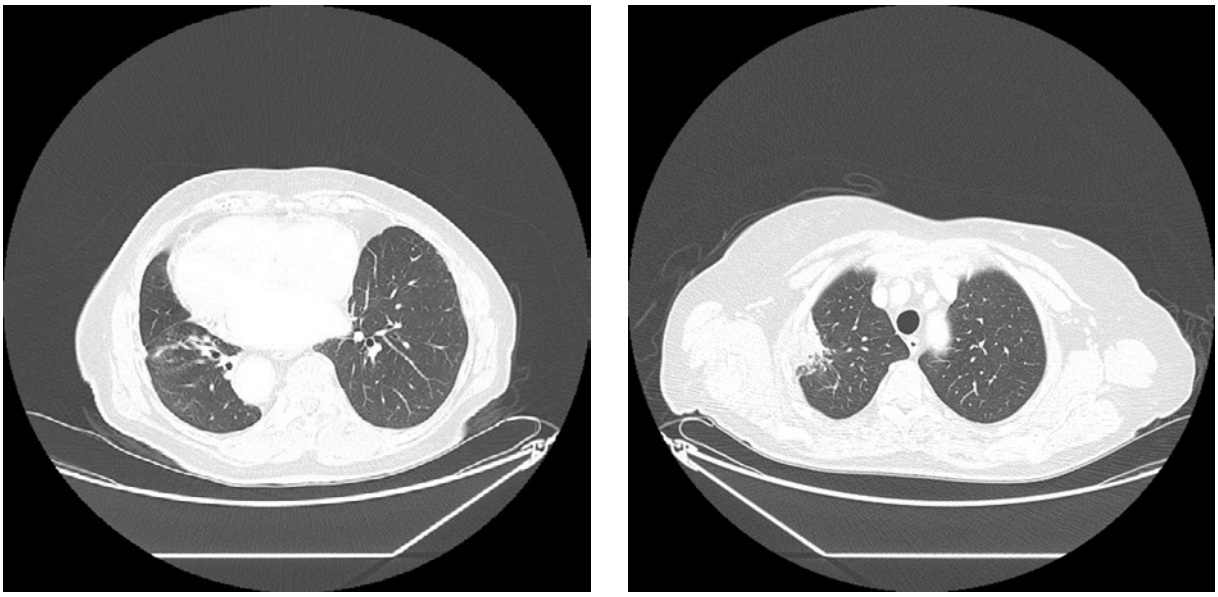

Figure 3. Lung metastases CT scan images of patient treated with vismodegib due to BCC, 29.08.2017 (description in the text)

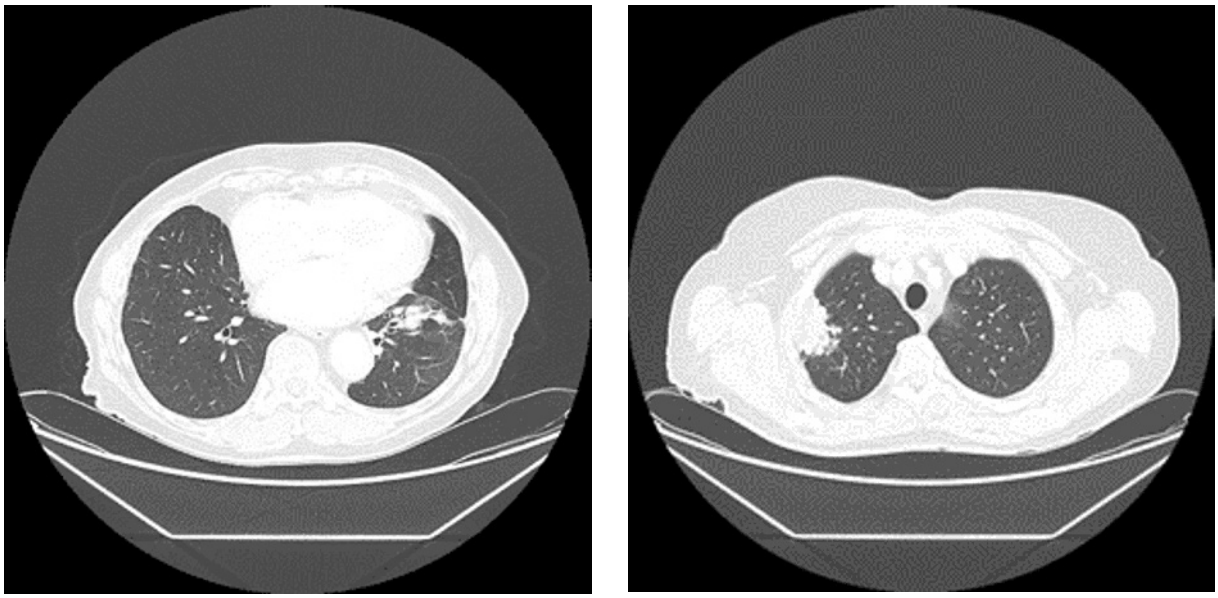

Figure 4. Lung metastases CT scan images of patient treated with vismodegib due to BCC, 31.10.2017 (description in the text)

tients with basal cell carcinoma with distant metastases are a relatively small group of patients with BCC, but the treatment options in this group of patients are significantly limited [3]. The development of new therapeutic methods, including drugs targeting molecular pathways such as the hedgehog pathway, is a significant advancement in the treatment of these patients [4, 5]. The results of previously published clinical trials with vismodegib (ERIVANCE, STEVIE) and sonidegib (BOLT) indicate that these medicines give the response with good tolerability [6–16]. The cases of patients presented here, a patient with locally advanced cancer and a patient with cancer in the generalised setting, confirm that this treatment can be effective and well tolerated [6–18]. It should be remembered that although the use of vismodegib is a significant advance in BCC-targeted therapy, cases of primary and secondary resistance to this drug have been observed. Patients undergoing treatment with this drug require regular assessment of efficacy and tolerability. It should be emphasised that also numerous cases of the

emergence of SCC within BCC during treatment with vismodegib have been described.

Vismodegib is an orally administered small molecule inhibitor of the hedgehog pathway. The transmission of hedgehog signals via SMO (smoothened transmembrane protein) leads to the activation and localisation of GLI (glioma-associated oncogene) transcription factors in the cell nucleus and the induction of target hedgehog pathway genes. Many of these genes play a role in cell proliferation, survival, and differentiation. Vismodegib binds to the SMO protein and inhibits its function, leading to blockade of signal transmission through the hedgehog pathway [1, 15, 19–23].

Vismodegib was approved by the FDA in January 2012 for the treatment of patients with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery, or who are not candidates for surgery, and who are not candidates for radiation, based on a study in which 104 patients participated.

The first clinical trial designed to asses of the safety and efficacy of vismodegib in the treatment of patients with BCC was ERIVANCE (NCT00833417), an international, multicentre study with one group and two cohorts (n = 104) [7, 16]. Metastatic BCC (n = 33) was defined as BCC that spread beyond the skin to other organs, including lymph nodes, lungs, bones, and visceral organs. Patients with locally advanced BCC (n = 71) were limited to those who could not be operated (inoperable, numerous recurrent lesions, for which cure by resection was considered unlikely or for which surgery would result in a significant deformity or morbidity) and for whom radiotherapy was ineffective or contraindicated or was considered an inappropriate method of treatment. Before the inclusion in the study, the diagnosis of BCC was confirmed by pathology test. Patients took orally vismodegib at a dose of 150 mg per day. The treatment was continued until disease progression, unacceptable toxicity, or consent withdrawal by the patient from further participation in the study. The primary endpoint was the objective response rate assessed independently; the secondary endpoints included response rate assessed by investigators, duration of response, progression-free survival (PFS), overall survival (OS), change in symptoms reported by the patient in comparison to day 1, the safety of treatment, and the lack of residual disease in the group of patients with locally advanced cancer. In the analysis of the results, 39 months after inclusion into the study of all patients, median duration of treatment with vismodegib was 12.9 months (0.7–47.8 months), in the group of patients with metastatic disease it was 13.3 months. (0.7––39.1 months), and in the group with locally advanced BCC it was 12.7 months (1.1–47.8 months). The response rate based on the investigators assessment was 48.5% in the group of patients with metastatic cancer and 60.3% in patients with locally advanced disease. Median duration of response was 14.8 months in patients with metastatic cancer and 26.2 months in locally advanced cancer. The one-year survival rates in groups of cancer patients with metastases and locally advanced cancer were 78.7% and 93.2%, respectively, and the two-year survival rates were 62.3% and 85.5%, respectively. The most commonly reported adverse events (in all degrees of severity) during the treatment included muscle spasms (71.2%), alopecia (66.3%), dysgeusia (55.8%), weight loss (51.9%), fatigue (43.3%), and nausea (32.7%). Adverse events of at least grade 3 were observed in 58 patients (55.8%), the most common of which were weight loss and muscle spasms. Serious adverse events were observed in 36 patients (34.6%), whereas in nine cases their causal relationship with the use of vismodegib (8.7%) was recognised. These events included pneumonia (n = 4), syncope (n = 4), hip fracture (n = 3), death (n = 3), heart failure, cellulitis, gastrointestinal bleeding, squamous cell cancer, pulmonary embolism, and venous thrombosis. The occurrence of adverse events was observed more frequently in patients treated with vismodegib for at least 12 months; however, the risk of new adverse events after the first year of treatment was lower [7, 16].

The safety and efficacy of the drug was confirmed in the next clinical trial, STEVIE (NCT 01367665), which enrolled 1232 patients with locally advanced BCC not eligible for surgical treatment and metastatic BCC, from June 2011 until September 2014 (in 167 centres in 36 countries) [8, 9, 13, 14]. Seventeen patients included in the study were excluded from the analysis of safety and efficacy. Ultimately 1215 patients were included in the analysis, including 1119 patients with locally advanced BCC and 96 patients with metastatic cancer. In this multicentre open-label clinical trial, the participants were adults, in good performance status (ECOG 0–2), with normal visceral organs function. Patients received vismodegib orally at a dose of 150 mg per day in 28--day cycles. The treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent for further participation by the patient. The primary endpoint was the safety of vismodegib. The efficacy evaluation parameters belonged to secondary endpoints. The median duration of treatment was 8.6 months (range 0–44). In the majority of patients at least one treatment-related adverse event (98%) was observed, the most frequent ones being similar to those reported in previous analyses. Serious adverse events related to the treatment were observed in 289 patients (23.8%). Taking the medicine for over 12 months was not associated with increased incidence or severity of adverse events associated with the treatment. Most of the adverse events persisting after the end of treatment

subsided within the next 12 months. The reported response rate was 68.5% (95% CI 65.7–71.3) in patients with locally advanced cancer and 36.9% (95% CI 26.6–48.1) in patients with metastatic disease.

The most frequently observed side effects of vismodegib, observed in at least 10% of patients, included muscle cramps, alopecia, dysgeusia, weight loss, fatigue, loss of appetite, upper respiratory tract infections, nusea, vomiting, diarrhoea, constipation, joint pain, and lack of taste sensation.

In addition to vismodegib, the safety and efficacy of a second inhibitor of the hedgehog pathway, sonidegib, was also evaluated in the treatment of BCC patients. In a phase 2 randomised trial of BOLT acronym (NCT 01327053), 230 patients were randomly assigned to treatment with sonidegib in a dose of 200 mg (n = 79) or in a dose of 800 mg (n = 151). Objective response rates in the groups treated with the doses of 200 mg and 800 mg were 57.6% and 43.8%, respectively, in patients with BCC in the locally advanced stage and 7.7% and 17.4% in the metastatic disease. Of the 94 patients with locally advanced disease, 18 resulted in progression or death, and in more than 50% of patients the response lasted for more than six months. In four out of five patients who responded to treatment, this response was sustained. Adverse events grade 3 and 4 and adverse events requiring treatment discontinuation were less frequently observed in the group treated with the lower dose of sonidegib (38.0% *vs*. 59.3% and 27.8% *vs*. 37.3%, respectively) [11].

Summary

New treatment options for patients with basal cell carcinoma that is beyond the scope of local treatment (radiotherapy, surgery) including, among others, vismodegib and sonidegib represent a significant advance in treatment. According to the Minister of Health's announcement from December 2016 vismodegib is a reimbursed therapeutic option in Poland in this patient group within the drug access program that was implemented in January 2017. The inclusion for treatment in this program is the fulfilment of all criteria, including the approval of the committee appointed by the National Health Fund. Sonidegib, despite being approved in the EU, has not yet been approved for refund in Poland.

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