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Systemic treatment of patients with solid tumors during the COVID-19 (SARS-CoV-2) pandemic — comprehensive recommendations of the Polish Society of Clinical Oncology

Introduction

The COVID-19 (SARS-CoV-2) pandemic has become a reality and there is an increasing number of people infected and dead from COVID-19 day by day in Europe. At the time of publication of this study, there were already one million new cases and over 50,000 deaths reported worldwide, and 2,700 and 51 in Poland, respectively [1]. The rapidly increasing burden on healthcare systems may soon be unbearable even for the best organized and funded ones. There is no doubt that in Poland, similarly to all countries, there are many unknowns regarding the duration of the pandemic, the dynamics of the increase in the number of patients requiring hospitalization or intensive care and the possibility of organizational support of rapidly growing health care needs. Over the past month, many hospitals in our country have been turned into so-called uniform infectious hospitals, being de facto closed for patients with diseases other than COVID-19. More and more cancer centers and units are limiting their activities due to staff infections or mandatory quarantine. Unfortunately, this situation leads to a growing problem of limited or complete lack of access to oncological treatment. For many patients diagnosed with malignant diseases, such a situation of indefinite duration may be tantamount to taking away chances for cure or a sharp deterioration in prognosis. There is no doubt that many patients without systemic anticancer treatment will have much worse prognosis than the vast majority of people infected with SARS-CoV-2. Cancer patients require special measures to protect them from infection and to establish diagnose early because the combination of both diseases is particularly unfavorable, not only due to the risk of infection-related death, but also considering, how difficulty is oncological treatment of a SARS-CoV-2 positive individual for the patients, as well as, healthcare system.

In response to the current situation and to safeguard the quality and continuity of therapy for cancer patients, the Polish Society of Clinical Oncology (PTOK, Polskie Towarzystwo Onkologii Klinicznej) has developed preliminary recommendations for oncologists [2]. Due to the huge number of questions and requests for more detailed recommendations regarding specific clinical situations, PTOK has developed specific therapeutic recommendations. We would like to highlight that

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this study does not apply to haemato-oncological and pediatric patients for whom the development of specific treatment recommendations is the responsibility of relevant societies.

COVID-19 in adults with solid tumors

It is widely known that elderly people with comorbidities represent the population at highest risk of complications and death due to SARS-CoV-2 infection [3]. Since the majority (> 60%) of cancer are diagnosed after the age of 65, and in Poland currently there are about a million people diagnosed with cancer (including a large group undergoing active treatment), there is no doubt that this is a special risk population. Available information on the course of COVID-19 in cancer patients is very limited and based on 2 publications including a total of 46 patients [4, 5]. In the most recent publication Liang et al. analyzed the data of 1590 patients with COVID-19 and 18 (1%) patients in the group had a history of cancer; this percentage was over 3 times higher than in the general Chinese population (0.29%). The majority of patients included in the analysis were people during post-treatment follow-up, while 6 patients underwent active systemic therapy (2 — targeted therapy of lung cancer, 2 — chemotherapy of lung cancer, 1 — immunotherapy of clear cell carcinoma, 1 — complementary systemic treatment of breast cancer of non-specified type). Serious complications associated with COVID-19 were observed much more frequently in the cancer group than in the general population (39% *vs.* 8%), however, cancer patients were older (mean age — 63.1 *vs.* 48.7 years) and were more often smokers (22% against 7%). In lung cancer patients who underwent chemotherapy or surgery within a month before the diagnosis of COVID-19, serious complications were more frequent than in patients during long-term follow-up (75% *vs.* 43% respectively). Based on logistic regression model it was shown that the risk of serious complications of COVID-19 was greater for people with positive oncological history (OR = 5.39) than with chronic obstructive pulmonary disease (COPD; OR = 3.39), diabetes (OR = 2.2) and hypertension (OR = 1.87). Zhang et al. analyzed a group of 28 patients with solid tumors diagnosed with COVID-19 and treated in three hospitals in Wuhan. The most common cancers in the analyzed population were lung cancer (25%), esophageal cancer (14.3%) and breast cancer (10.7%), and every third patient had stage IV disease. All patients had previous systemic treatment and 21% of them received therapy within 14 days prior to COVID-19 diagnosis (11% chemotherapy, 7% targeted therapy, 4% radiotherapy, 4% immunotherapy). In most patients, COVID-19 symptoms appeared while at home, and in 29% of patients this diagnosis was made during hospitalization. The most common symptoms were fever and cough (> 80% of patients). Severe complications of COVID-19 were observed in the majority (70%) of patients with generalized cancer and in 44% of patients with stage I–III. COVID-19 mortality in the analyzed patient population was 28.6%, which is almost 10 times higher than in the general Chinese population [6]. Multifactorial analysis indicated a four times higher risk of serious complications in patients who underwent oncological treatment within 14 days before the diagnosis of COVID-19 (HR = 4.079; 95% CI 1.086–15.332) [5].

As available literature is still scarce, it is difficult to draw unequivocal conclusions about the risk of severe course of COVID-19 in patients with cancer. However, it seems that higher risk group includes patients with generalized cancer during active oncological treatment. Nevertheless, it is difficult to say whether the location of the cancer, disease stage, or the type of anti-cancer treatment used is more important. In Liang et al. analysis there were no complications observed in the only patient (52 years) treated for breast cancer or in 3 patients treated for lung cancer (patients aged 55 and 58 years undergoing targeted therapy; 47-year-old patient undergoing chemotherapy). On the other hand, serious complications were observed in a 63-year-old patient receiving palliative chemotherapy for lung cancer and, surprisingly, in a 58-year-old patient undergoing immunotherapy for clear cell carcinoma [4].

Very limited scientific data does not allow to draw definitive conclusions regarding the principles of management in patients diagnosed with cancer in the context of the SARS-CoV-2 infection risk. There is no doubt, however, that the age of the patients, comorbidities, and anti-cancer treatment may increase the risk of serious complications and death during COVID-19.

Therefore, depending on the general condition of the patient, the nature of the planned or ongoing anti-cancer treatment and the clinical stage of disease, the principles of management during the SARS-CoV-2 pandemic should be differentiated.

Recommendations for systemic oncological treatment

Systemic treatment of cancer patients may be either radical (preoperative or postoperative treatment, chemotherapy alone in the case of chemo-sensitive tumors, chemotherapy in combination with irradiation) or palliative. We believe that it is essential to strive to maintain the recommended intensity of radical treatment. Each time, if it is not possible to continue the systemic treatment already introduced with a radical intention, the patient must be urgently transferred to

another functioning clinical oncology center in a given province in order to continue treatment. The list of such centers is available through voivodship clinical oncology consultants. In case of palliative therapy, care should be taken not to remarkably deteriorate the patient's chances of maintaining disease control, while reducing the exposure to infectious agents; achieving this goal may require modification of the regimen, dosage or the drug used.

Preoperative treatment

The decision of a multidisciplinary board to initiate preoperative treatment always takes into account the planned date of surgery. For patients with breast cancer, when the goal of preoperative treatment is to perform breast-conserving surgery (especially in postmenopausal women [7]), it is possible to consider postponing the start of preoperative chemotherapy for several weeks and more widely use preoperative hormone therapy (postmenopausal patients). In patients with primarily operable tumors in whom preoperative chemotherapy has no proven effect on improving prognosis, surgery should be performed first, followed by systemic adjuvant treatment. On the other hand, in all patients with significant local advancement of the disease, when the goal of neoadjuvant treatment is to achieve the possibility of surgery or radical radiation therapy, the procedure should be started without undue delay. In patients undergoing preoperative chemotherapy, when significant (many weeks) delay of surgery is expected, it is recommended to consider 1–2 additional cycles of chemotherapy according to the last used regimen. It should be ensured that there are no absolute contraindications for continuing chemotherapy (current tolerance, cumulative toxicity). If there are any doubts related to the possible "extension" of preoperative treatment, this situation could be consulted with team of consultants from the Department of Oncology, JU-CM, Krakow (chemioterapia@su.krakow.pl). Proposals for the management of pre/perioperative treatment are presented in Table 1.

Postoperative treatment

In majority of patients the initiation of systemic adjuvant treatment can be postponed and started within 2 (in justified cases — 3) months after surgery. The exception are patients with very high risk of recurrence (e.g. significant local stage, triple-negative breast cancer). In justified clinical situations, adjuvant treatment may be replaced by close observation. In patients with hormone-dependent breast cancer (especially with low malignancy grade [G1] and/or low proliferative index [Ki67 < 30%] or with types of better prognosis), where the potential benefit of chemotherapy may be small, adjuvant hormone therapy alone should be considered. If there any some doubts regarding the possibility/legitimacy of resigning from complementary chemotherapy, it is possible to consult patients with the consulting team of the Department of Oncology, JU-CM in Krakow (chemioterapia@su.krakow.pl). Proposals for modification of adjuvant treatment are included in Table 1.

Palliative treatment

Unlike therapy with radical intention, palliative systemic treatment, especially in the later lines, commonly based on less powerful evidence from large randomized clinical trials or meta-analyses. This treatment consists mainly of available in a given indication and active cytotoxic drugs used alone or in combination. In most cases, the way of conducting long-term, multi-stage palliative treatment is based on available literature data with relatively low scientific credibility and the own experience of individual oncological centers. As the duration and extent of the SARS-CoV-2 pandemic are indefinite, there is impossible to predict how long the implementation of exceptional rules for managing cancer patients will be necessary. In this context, the most questions regarding optimal management regard patients requiring chronic cancer therapy. There is no doubt that long-term suspension of systemic treatment increases the risk of disease progression, which may result in a significant deterioration of performance status and functional capacity of organs. It is therefore important to be aware that the long-term deterioration of oncological care during a pandemic can significantly worsen patients prognosis, to an unpredictable extent.

For the above reasons, PTOK's statement regarding the modification of palliative treatment, in the situation of complete uncertainty as to the scale and duration of the epidemic threat, is an attempt to find optimal solutions that allow in the several months to ensure the maximum possible safety of the patient and disease control.

Proposed modifications of systemic treatment with palliative intention

— Chemotherapy
- asymptomatic patients with good disease control and no risk of organ "crisis" — the possibility of discontinuing chemotherapy ("therapeutic holidays"), reducing the intensity of therapy (extending the intervals between courses by 50–100%) or implementing systemic treatment using available oral drugs (including metronomically used) should be considered;
- patients with deep or long-lasting remission during maintenance chemotherapy — periodic discontinuation of treatment should be considered;

Table 1. Modification of systemic therapy regimens in radical treatment

	Management options	Comment
Esophageal cancer	Perioperative treatment	
	Preferred CROSS protocol without modification (5 cycles of PXL 50 mg/m^2 + CBDCA AUC 2; all cycles q1w) — least exposure to other patients [8] For adenocarcinomas of the lower esophagus consider perioperative chemotherapy without radiation (as in gastric cancer)	CROSS protocol: a total of 5 + 23 RT fractions For comparison, the PF scheme is associated with greater exposure to contact with other patients. PF scheme: a total of 8–10 days of inpatient chemotherapy + 23–28 RT fractions
Gastric cancer	Perioperative treatment	
	FLOT (4 cycles before and after surgery: DXL 50 mg/m^2; OXA 85 mg/m^2; leucovorin 200 mg/m^2; 5-FU 2600 mg/m^2) q2w — preferred option CAPOX (3 cycles before and after surgery: OXA 85 mg/m^2; capecitabine 2000 mg/m^2 d1–14 or 1330 mg/m^2 d1–21)	FLOT regimen: a total of 16 days of inpatient chemotherapy — the preferred option with higher efficiency (the possibility of halving the length of hospitalization by using a home infusion device for long 5-FU infusions) CAPOX regimen: a total of 6 outpatient chemotherapy — a less effective option, dedicated to patients with reduced performance status, to consider in patients with good performance status when no hospital beds and infusors are available and there is no possibility to redirect the patient to another center No data on the efficacy of the FLOT regimen equivalent with capecitabine (only data on acceptable safety and activity in metastatic disease in phase I and phase II studies) — such modification is not recommended [9] Consider a larger number of cycles in the preoperative period at the expense of the postoperative (e.g. 6 × FLOT → resection → 2 × FLOT) —- with the option of giving the entire treatment before surgery when a timely operation is not possible
Pancreatic cancer	Adjuvant chemotherapy	
	mFOLFIRINOX (12 cycles IRI 150 mg/m^2; OXA 85 mg/m^2; leucovorin 400 mg/m^2; 5-FU 2400 mg/m^2) q2w — preferred option — keep the assumed dosage intensity [10] Gemcitabine (1000 mg/m^2) ± capecitabine (1650 mg/m^2) d1, 8 every 21 days	mFOLFIRINOX is the regimen of the highest effectiveness, preferred in patients in good performance status (PS) (it is possible to halve the length of hospitalization by using a home infusors device for long 5-FU infusions) GEM-CAP regimen is the second choice option in patients in good PS when no hospital beds and infusors are available and there is no possibility to redirect the patient to another center In 2 retrospective studies, the benefit of adjuvant therapy was still shown despite its implementation > 12 weeks after resection [11, 12] consider delaying the start of adjuvant treatment for 4 months after resection, especially in patients with slow recovery
HCC	Non-surgical treatment	
	Embolization of the hepatic artery alone seems no less effective than chemoembolization or radioembolization — an option when appropriate preparations are not available [13]	If definitive treatment (resection, embolization) is not available during the epidemic — sorafenib (400 mg bid) as a bridging option, preventing progression to the resumption of planned surgeries
Bile duct cancer	Adjuvant chemotherapy	
	Capecitabine (8 cycles 2500 mg/m^2; d1–14; q3w) — in case of good tolerance of the first 2 cycles — option of dispensing the medicine for 2–3 cycles and tolerance control via telemedicine	In patients with abnormal kidney function (CrCl 50–30 mL/min) — the capecitabine dose must be reduced to 75%, for CrCl < 30 mL/min — do not use capecitabine

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Table 1. cont. Modification of systemic therapy regimens in radical treatment

	Management options	Comment
Colon cancer	Adjuvant chemotherapy	
	Shift from the Mayo regimen (5-FU bolus) to capecitabine, also in combination with radiotherapy in rectal cancer [14]. It is possible to dispense the medicine for the entire 5 weeks at once in case of combined radiochemotherapy Do not use radiochemotherapy with oxaliplatin in rectal cancer. This is more toxic and its beneficial effect on OS has not been proven [15] Adjuvant chemotherapy with capecitabine (8 cycles 2500 mg/m^2; d1–14; q3w) — in case of good tolerance of the first 2 cycles — option of dispensing the medicine for 2–3 cycles and tolerance control via telemedicine In patients pT3 N1 consider only four XELOX cycles [16, 17]	The Mayo regimen is more toxic and generates more visits than treatment with capecitabine Serious complications will affect no more than 20% of patients taking capecitabine [18] In the stage, II consider only observation, except the patients for extremely poor prognosis (T4N0) In patients with abnormal kidney function (CrCl 50–30 mL/min) — the capecitabine dose must be reduced to 75%, for CrCl < 30 mL/min — do not use capecitabine
Breast cancer	Adjuvant chemotherapy	
	Luminal HER2-negative • intermediate risk — 4 × TC (docetaxel 75 mg/m^2 + cyclophosphamide 600 mg/m^2* q3w) [19, 20] • high risk [21, 22] — **4 × ddAC** (q2w) → 4 × docetaxel 75–100 mg/m^2* (q3w)** — 4 × docetaxel 75–100 mg/m^2* (q3w) → 4 × ddAC** (q2w) HER2-positive • **6 × TCH (docetaxel 75 mg/m^2 + carboplatin AUC6 + trastuzumab)* q3w** [23] • 4 × ddAC** (q2w) → 4 × docetaxel 75–100 mg/m^2* + trastuzumab (q3w) [22, 24] Triple-negative breast cancer (TNBC) • **4 × ddAC** (q2w) → 12 × paclitaxel 80 mg/m^2* (q1w)***** [22, 25]	PREDICT tool (https://breast.predict.nhs.uk/) allows you to estimate the benefit of chemotherapy in the context of overall survival. Considering the benefit against the risk of distant complications, it seems that the benefit up to 3–4 percentage point (p.p.) does not justify the use of chemotherapy, in the case of intermediate risk the benefit is usually 4–6 p.p., and at high risk the estimated benefit of chemotherapy exceeds 7 p.p. For patients with pN0–pN1 stage with a complex tumor phenotype (especially G2, with low or medium hormone sensitivity, borderline Ki67 10–40% or an unusual phenotype, e.g. G1 with high Ki67) optimal risk estimation is obtained using the Magee calculator (https://path.upmc.edu/onlineTools/MageeEquations.html). It captures the percentage of Ki67 in tumor meshwork, the degree of differentiation with the score breakdown to nuclear pleomorphism, mitotic index and tubular structure (3–9 points, where 3–5 points correspond to G1, 6–7 points corresponds to G2, 8–9 points corresponds G3, Nottingham system according to Scarff-Bloom-Richardson modified by Elston-Ellis). Magee allows an approximate estimation of the Recurrence Score, which can be obtained using the Oncotype DX genomic test. In case of values < 11 points patients can be safely withdrawn from chemotherapy. In turn, the result > 25 points indicate high risk and is an indication for chemotherapy Patients with ≥ pN2 stage — always belong to the highrisk group and must receive chemotherapy For all triple-negative and high-risk HER2-positive and HER2-negative cancers (≥ pN2), adjuvant chemotherapy should be started within 30 days of surgery Adjuvant treatment regimens recommended for use in preoperative chemotherapy are marked in bold In case of high-risk, HER2-positive breast cancer adding pertuzumab to preoperative treatment is recommended If paclitaxel 80 mg/m^2 cannot be used weekly, docetaxel 100 mg/m^2 every 3 weeks should be given (+ long-acting growth factor [granulocyte-colony stimulating factor, G-CSF]) The adding of carboplatin to standard preoperative chemotherapy in patients with triple-negative breast cancer increases the likelihood of a pathological complete response (pCR) regardless of harbouring *BRCA1/2* mutation. However, this approach increases the toxicity of chemotherapy and should be reserved only for patients with significant local advancement

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Table 1. cont. Modification of systemic therapy regimens in radical treatment

Lung cancer	Adjuvant chemotherapy	
	Modified regimen PN: cisplatin 75–80 mg/m^2 + vinorelbine 25–30 mg/m^2 d1 + vinorelbine (tab) 60 mg/m^2 d8 — q3w [26] Sequential radiochemotherapy (locally advanced stage) wit regimen PN: cisplatin 75–80 mg/m^2 + vinorelbine 25–30 mg/m^2 d1 + vinorelbine (tab) 60 mg/m^2 d8 — q3w	In case of contraindications to the use of cisplatin as part of adjuvant postoperative chemotherapy, replacement by carboplatin is not recommended and patient should be only closely monitored. No literature data support any benefit of carboplatin in the adjuvant setting in patients with non-small cell lung cancer Vinorelbine tablets can be dispensed on day 1
Gynecological cancers	Preoperative treatment	
	There are no data on the possibility to modify the recommended adjuvant treatment regimens in ovarian and endometrial cancer	
Bladder cancer	Pre- or postoperative treatment	
	4 AMVAC courses — methotrexate 30 mg/m^2, vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2 cisplatin 70 mg/m^2 (4-hours infusion)** d1 — cycle repeated every 14 days [27]	AMVAC chemotherapy (accelerated MVAC) reserved for patients in good general condition (so-called fit for chemotherapy). Preferred preoperative treatment. In case of any doubts regarding the possibility of using postoperative chemotherapy — leave patients under observation
Upper urinary tract cancer	Adjuvant chemotherapy	
	4 courses with cisplatin 70 mg/m^2 + gemcitabine 1000 mg/m^2 d1, 8 every 21 days	In patients with GFR ≥ 30 and < 50 mL/min — carboplatin may be used [28] In case of any doubts regarding the possibility of administering full 4 courses — leave patients under observation If there is a need to extend the intervals between courses — the treatment should be discontinued [28]

*Short-acting growth factor (G-CSF); **long-acting growth factor (G-CSF); q1w — every week; q2w — every 2 weeks; q3w — every 3 weeks; bid — 2 times a day

- patients requiring maintenance of continuous systemic treatment (organ "crisis" threat, symptoms, recently started treatment) receiving chemotherapy based on regimens administered at 3-week intervals — treatment should be continued with the chosen regimen;
- patients receiving weekly regimens — it is recommended to modify to 2- or 3-weekly regimens (increase the dose of the drug) or to modify to doublet regimen used every 2–3 weeks. Examples of weekly regimens modifications are presented in Table 2;
- In selected patients, with satisfactory tolerability and efficacy of oral chemotherapy, drugs can be dispensed on more than one treatment cycle. The prerequisite for this is the possibilit to perform adequate blood tests in the district outpatient clinic, and phone verification of results and subjective tolerance of therapy at the beginning of each course.

— Molecularly targeted treatment
  - patients taking oral molecularly targeted drugs with good previous treatment tolerance — dispensing medication for a maximum of 6 months provided that they maintain regular remote contact with the attending physician and that there is the possibility of blood tests at the place of residence;
  - patients receiving intravenous molecularly targeted drugs (mainly monoclonal antibodies) — the need to maintain therapy with the possibility of reducing its intensity according to Table 3.

— Hormonotherapy — it is necessary to continue hormone therapy in accordance with standards, it is not recommended to stop or delay the administration of drugs regardless of the form of their use (oral, intramuscular, subcutaneous). In the case of gonadoliberin analogues — patients should receive injections outside the oncological centers.

Table 2. Exemplary modifications of chemotherapy regimens in palliative treatment

Regimen	Proposed modification
Paclitaxel 80 mg/m^2 weekly	Paclitaxel 120 mg/m^2 every 2 weeks [29]
Gemcitabine 1000 mg/m^2 d1, 8 every 21 days Gemcitabine 1000 mg/m^2 d1, 8, 15 every 28 days	Gemcitabine 1250 mg/m^2 every 2 weeks *Gemcitabine 1000 mg/m^2 every 2 weeks if there is a problem in maintaining the earlier dosage*
Cisplatin 25–30 mg/m^2 weekly	Cisplatin 50 mg/m^2 every 2 weeks Cisplatin 75 mg/m^2 every 3 weeks
Cisplatin 25 mg/m^2 + gemcitabine 1000 mg/m^2 d1, 8 every 21 days	Cisplatin 35 mg/m^2 + gemcitabine 1250 mg/m^2 every 2 weeks
Cisplatin 70 mg/m^2 d1 + gemcitabine 1000 mg/m^2 d1, 8, 15 every 28 days	
Vinorelbine 25 mg/m^2 *i.v.* or 60–80 mg/m^2 weekly	Vinorelbine 50 mg *p.o.* (Monday, Wednesday, Friday) [30] or 30 mg *p.o.* every 2nd day (in the elderly) — cycles every 2–3 weeks [31, 32]
Carboplatin 2 AUC *i.v.* weekly	Carboplatin 5–6 IV AUC every 3 weeks
Capecitabine dosage d1–14 every 21 days	Capecitabine — continuous mode (66% of the standard daily dose for 14/21 cycle) visits every 6 weeks

Table 3. Optimization of intravenous targeted therapies use

Breast cancer	Docetaxel + trastuzumab + pertuzumab	Pertuzumab + trastuzumab — after 6 courses with docetaxel — dosing at intervals of up to 6 weeks [33, 34] (no need for loading doses)
	Trastuzumab + chemotherapy (different drugs)	Trastuzumab (up to every 6 weeks) + monotherapy or combinations of metronomically used drugs [35]
	Trastuzumab emtansine	Intervals up to every 6 weeks [36]
Ovarian cancer	Paclitaxel + carboplatin + bevacizumab	Recommended intervals up to every 4 weeks — *no clear data on the possibility of using longer intervals* [37, 38]
Colon cancer	FOLFOX + panitumumab FOLFIRI + cetuximab	Intervals up to every 4 weeks [39, 40]. In patients with an objective response (according to the provisions of the drug program) — interruption of the treatment or chemotherapy alone (without anti-EGFR) — FOLFIRI/FOLFOX (up to every 5 weeks), alternatively capecitabine alone. *The use of monotherapy with anti-EGFR antibodies — is less active than the combination of anti-EGFR antibody with 5-FU/LV* [41]
	FOLFIRI/FOLFOX + bevacizumab	Courses every 4 weeks. *The use of monotherapy with anti-VEGF antibodies — is less active than combination of anti-EGFR antibody with 5-FU/LV* [42]
	FOLFIRI + aflibercept	Courses every 4 weeks [43]
Gastric cancer	Capecitabine/5FU + cisplatin + trastuzumab	Use of trastuzumab at intervals of up to 6 weeks + capecitabine monotherapy [44]
Renal cancer	Temsirolimus	There is no conclusive data on the possibility of delay — intervals of up to 2 weeks may be considered [45–47]

— Immunotherapy with immune checkpoint inhibitors
  - in patients with complete response lasting at least 24 months — treatment interruption and observation;
  - in patients with objective response lasting for more than 6 months to consider a maximum 2-fold extension of the intervals between courses;
  - patients with stabilization or deepening response — continuation of treatment according to the standards.

If there are any doubts regarding the possibility of dose modification, it is possible to contact the consulting team of the Department of Oncology, JU-CM in Krakow (chemioterapia@su.krakow.pl).

Neutropenic fever in the course of cancer treatment

Due to the fact that symptomatic SARS-CoV-2 infection manifests with high fever, it is difficult to distin-

guish the first symptoms of COVID-19 from neutropenic fever without performing diagnostic tests. According to current recommendations, patients with suspected COVID-19 (at least one of the symptoms: **fever,** cough, shortness of breath) should be isolated in properly equipped rooms (sluice room, personal protective equipment, pulse oximeter, thermometer, access to medical gases, resuscitation kit)) and then subjected to further diagnostics [9]. There is no doubt that in the current situation every patient with symptoms suggestive of COVID-19 (also with only "classic" neutropenic fever) can seriously disrupt the functioning of the entire healthcare unit and disorganize the work of medical staff. Therefore, in order to minimize the risk of neutropenic fevers in patients undergoing chemotherapy, it is recommended to use prophylactically G-CSF for the duration of the COVID-19 (SARS-CoV-2) pandemic:

— in all patients receiving chemotherapy at intermediate risk (10–20%) of neutropenic fever;
— in all patients receiving chemotherapy, who had episode of neutropenia grade 3 according to CTC-AE (< 1000/mm^3) during the current regimen.

Corticosteroids in premedication and treatment of complications

Corticosteroids in clinical oncology are most often used to prevent the side effects of chemotherapy (nausea, vomiting, anaphylactic reactions) or targeted drugs (prevention of mineralocorticoid excess syndrome during abiraterone acetate therapy). These drugs are also sometimes necessary to maximize the anti-cancer effect (prednisone with docetaxel in the treatment of castration-resistant prostate cancer or multi-drug hematology regimens. In recent years, corticosteroids have also become the key medicines used to neutralize the autoimmune complications of immunotherapy with immune checkpoint inhibitors, which often are life-threatening. However, since corticosteroids have a strong immunosuppressive effect, a lot of controversies has arisen about the safety of these drugs in the context of COVID-19.

Available literature data indicate that **there are no significant risks associated with the use of corticosteroids in patients infected with SARS**. These drugs were widely used during the SARS-CoV and MERS-CoV epidemics [48, 49]. In a retrospective analysis of 401 critically ill patients diagnosed with SARS-CoV infection, corticosteroids reduced mortality and hospitalization time, without increasing the risk of secondary infections and other complications [50]. Available publications covering patients with MERS-CoV, SARS-CoV and RSV infections indicate that corticosteroids may delay the time of virus elimination from the body and induce typical complications, but have a beneficial effect on reducing the inflammatory process and lung tissue damage [48, 51]. WHO guidelines do not recommend routine use of corticosteroids in all patients diagnosed with COVID-19 [52]. According to current recommendations in patients with SARS-CoV-2 infection requiring corticosteroids (inhaled or systemic) their administration should not be interrupted, but dose reduction may be considered [53]. Therefore, corticosteroids in cancer patients without SARS-CoV-2 infection should be used in accordance with medical practice.

Patients with dyspnea without other clinical signs of infection

Patients reporting with dyspnea, which was not present before the pandemic onset, require extended diagnostics. If there are no other clinical symptoms suggestive of an infectious background, a chest CT scan should be performed and a SARS-CoV-2 test should be considered in accordance with current Chief Sanitary Inspector (Główny Inspektor Sanitarny, GIS) guidelines and the standards of health care unit. When radiological features suggesting interstitial pneumonia are present or difficult to differentiate from interstitial tumor involvement, a SARS-CoV-2 infection diagnostic should be performed and the patient should be isolated. In a patient without evident radiological symptoms, it is also important to urgently exclude the risk of pulmonary embolism.

Reuse of personal protective equipment

An essential element of health care during an epidemic is adequate protection of both staff and patients against secondary infection. Currently, all healthcare providers in the world are facing the problem of insufficient supplies of single-use personal protective equipment, and this problem especially applies to FFP2 and FFP3 masks. However, there are some possibilities for multiple use of protective masks through their appropriate disinfection. Such approach is usually contrary to the characteristics of the discussed medical products and based on low-class evidence. In the current epidemiological situation, however, it may be the only alternative that allows securing medical staff during patient care.

Protective mask is defined as a filtering protective mask in the FFP2 or FFP3 class (in the US terminology N95 and N99, respectively). According to the current guidelines, protective masks are disposable medical devices that should be exchanged between each individual contact with patient and attempts to reuse or disinfect them are possible only in exceptional situations, in accordance with internal hospital recommendations.

Prolonged use is defined as the use of one protective mask without removing it between subsequent patients, assuming that all patients are infected with one

pathogen. The maximum duration of use is difficult to determine — experience shows that FFP2 and FFP3 protective masks can be used for approx. 8 hours. This time is also preferred when protective masks are reused.

Decontamination of protective masks in the FFP2 and FFP3 class is not allowed in standard situations and can only be used in emergency situations after it has been approved by the personnel responsible for the epidemiological policy. Data on the possibility of decontamination of protective masks are based on the assessment of their protective properties against pathogens other than SARS-CoV-2. Available data confirm that a temperature of 70 degrees applied for 30 minutes is an effective method of destroying previously tested forms of SARS-coronavirus [54]. It is also important, that viruses survival time on external surfaces is limited and, depending on the material, ranges from 4–72 hours.

Any method used can have a negative effect on both the protective properties and structure of the mask, which can lead to leakage, therefore, a leak test should be carried out after every wearing a mask. The reuse of masks is associated with an increased risk of infection in case of a decrease in filtration efficiency or incomplete decontamination.

Based on the data on virus survival, it is possible to reuse the face mask by staff after a downtime of 5 days. In this situation, each employee exposed to the virus receives 5 masks signed with their name, each of which is used for 1 day, and then stored in a paper bag for 5 days. If there are not enough masks, it is possible to consider one of the decontamination methods (Table 4).

Based on the available data, the method of heating the mask for 30 minutes in the oven air heated to 70–75°C or use of UV disinfection for 30 minutes can be considered as a preferred method in conditions of limited availability of specialized equipment.

Summary

The recommendations of the Polish Society of Clinical Oncology and their brief summary (Table 5), in the absence of adequate, strong scientific evidence for management during COVID-19 (SARS-CoV-2) pandemic, reflects the authors' opinions. The PTOK position and help offered by the consultancy team of the Oncology Department of the Jagiellonian University-Collegium Medicum in Krakow are aimed at supporting decision-making clinical oncologists in this extremely complicated situation in which they find themselves.

As doctors, we must remember that our own and our colleagues' safety is a critical factor in the possibility of providing continuous care to our patients. As clinical oncologists, in many cases coordinating and binding oncological treatment, we may be forced in this extraordinary situation to make extraordinary decisions, extraordinary commitment, extraordinary effort. At the same time, we must remember that we have in our hands the fate of the patients, in whom we cannot miss the chance to be completely cured, as well as of patients with advanced disease, in whom our decisions should not worsen the prognosis.

Table 4. Methods of decontamination of FFP2 and FFP3 masks

Decontamination method [55–57]	Filtration efficiency/ /safe number of decontamination	Comment
Methods recommended by the CDC (Centers for Disease Control and Prevention) [58]		
Vaporous hydrogen peroxide (VHP)	High/20	Adequate infrastructure is needed
UV (sterilization chamber, 0.5–1.8 J/cm^2), 30 minutes	High/10	Adequate infrastructure is needed
Moist heat sterilization (min. temp. 60° C and 80% relative humidity), 15–30 minutes	High	Adequate infrastructure is needed
Other methods		
Hot air (oven), 70–75°C, 30 minutes	High/20	Risk of mask deformation (depending on the material used)
Steam > 160°C	High/3	A significant decrease in effectiveness after 5 procedures
75% alcohol, wetting and drying	Ineffective	The method should not be used
Chlorine containing solution, 5 minutes	Ineffective	The method should not be used
Gamma radiation (25 cGy)	No data	Risk of loss of tightness, access to the cyclotron necessary
Microwaves (microwave oven)	No data	All tested masks melted during the procedure

Table 5. PTOK recommendations in the context of the SARS-CoV-2 pandemic — summary

1. Recommendations for the management of systemic antitumor treatment during the COVID-19 (SARS-CoV-2) pandemic are not based on the results of prospective studies and to the greatest extent include observations regarding the management of other infections and expert opinions.
2. The most important element of the management is to prevent the spread of infection according to typical principles recommended in epidemic emergencies.
3. Systemic anti-cancer treatment should be carried out according to generally accepted principles.
4. Systemic treatment according to generally accepted principles should also include dealing with complications.
5. Systemic treatment according to generally accepted principles should be particularly observed in case of treatment with a radical intention.
6. Interrupting or abandonment of continued systemic treatment with a radical intention in a COVID-19 (SARS-CoV-2) pandemic situation is not scientifically justified.
7. Initiation of systemic adjuvant treatment may be replaced by close observation in strictly justified clinical situations. The use of one of the available methods or shortening the duration of the entire treatment should be considered.
8. Palliative systemic anti-cancer treatment should be continued, and it is possible to modify the regimens and doses depending on individual situations.
9. Modifications of palliative systemic anti-cancer treatment may include wider use of oral medications or metronomic treatment.
10. Preventive use of antiviral drugs has no scientific justification.
11. Granulopoietins prophylaxis during an epidemic emergency should be used in patients at intermediate risk of neutropenic fever.
12. Every patient with suspected COVID-19 before admission to the oncology center should have SARS-CoV-2 infection excluded in accordance with the applicable recommendations of the Chief Sanitary Inspectorate and the Ministry of Health.

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VIA MEDICA

ORIGINAL ARTICLE

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Retrospective assessment of Lung-RADS® performance in the Silesian Lung Cancer Screening Pilot Study

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ABSTRACT

Background. A high percentage of false positive results, observed in lung cancer screening studies with low-dose computed tomography (LDCT), caused the modification of radiological assessment methods. According to the International Early Lung Cancer Action Program (IELCAP) all non-calcified nodules with a dimension ≥ 4 mm were considered as positive. Implementation of classification the Lung CT screening Reporting and Data System (Lung-RADS®) recommends additional testing only for nodules ≥ 6 mm, which reduced of false positive results.

Methods. We provided a retrospective analysis of 601 LDCT scans, in asymptomatic volunteers of Pilot Silesian Study of Early Lung Cancer Detection, with at least 20 pack-years of cigarette smoking. The analysis of non- and invasive interventions was done. Assessment of nodules according to the Lung-RADS® system was done. Then the percentage of interventions that could be avoided using the Lung-RADS® criteria was estimated.

Results. In total, 1016 nodules were identified in 265 participants. The positive result of screening was defined as a presence of solid or part-solid nodule ≥ 5 mm and ≥ 8 mm in the case of a nonsolid nodule in line with the IELCAP protocol. Screening based on the IELCAP protocol resulted in 200 positive results and based on Lung-RADS® in the 116 positives. The frequency of lung cancers among participants with a positive result was 7 of 200 (4.0%) (95% CI: 1.0%, 6.0%) for IELCAP and 7 of 116 (6.0%) (95% CI: 2.7%, 9.3%) for Lung-RADS®. The Lung-RADS® criteria reduced number of non- and invasive procedures by 48.8% and 24.1%, compared to IELCAP protocol.

Conclusions. Adopting the Lung-RADS® classification system may reduce harms and improve the efficiency of lung cancer screening programs.

Key words: lung nodules, lung cancer screening, low dose computed tomography (LDCT), Lung CT Screening Reporting and Data System (Lung-RADS®)

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Introduction

Cancer is a leading cause of death worldwide, accounting for an estimated 9.6 million deaths in 2018. Screening programs aimed at detecting lung cancer target high-risk persons who need consistent monitoring to enable early diagnosis of the disease. The recommended screening test for lung cancer is low-dose computed tomography (LDCT) for persons who are at high risk of lung cancer because of cigarette smoking history and age [1]. In the case of detection of a pulmonary nodule, additional evaluations are needed to determine whether lung cancer is present. Screening protocols standardise interpretation of screen-detected nodules and harmonise nodule management. The International Early Lung Cancer Action Program (IELCAP) and the Lung CT screening Reporting and Data System (Lung-RADS®) are two protocols for lung cancer screening programs [2, 3]. The primary evidence of lung cancer screening effectiveness came from the National Lung Screening Trial (NLST) conducted without a protocol for management

of nodules [1]. The IELCAP showed that increased nodule size cut-offs decreased the fervency of positive results in the baseline screening, with only a few missed cancer cases [2, 4] in comparison to the method used in the National Lung Screening Trial [1]. It substantially reduced diagnostic workload. Most recently, the American College of Radiology introduced the Lung-RADS® protocol to reduce the frequency of false-positives without a significant effect on screening sensitivity [3, 5].

Population oriented screening for lung cancer has significant socio-economic consequences, especially for big countries with large populations of smokers. In Poland, there are about 8.7–9 million smokers (31% of adult men, of whom 26% smoke regularly, and 21% of adult women, of whom 17% regularly smoke) per 38.4 million inhabitants [6, 7]. Such a large-scale screening is a complex organisational challenge and is associated with both benefits and harms. Planning a screening program requires an optimal balance between the benefits, harms, and/or cost-effectiveness. Among many factors, categorisation of many small pulmonary nodules as negative screens substantially reduces the number of false-positives and the subsequent need for additional scans and invasive procedures.

The Pilot Silesian Study for Early Lung Cancer Detection with LDCT used IELCAP as the screening protocol [8]. To assess how the increase of the nodule size threshold would affect screening performance, we retrospectively applied Lung-RADS® criteria to nodule-level baseline results of the screening.

Material and methods

The Pilot Silesian Study included 602 asymptomatic adults with a history of tobacco smoking of at least 20 pack-years and former smokers who quit smoking within the last 15 years before the study visit. In our protocol 20 pack-years was adopted as the cut-off point, due to the inclusion in the cohort of people additionally exposed to other factors, *e.g.* occupational (miners, asbestos workers, steel workers) and environmental (air pollution in the areas of Upper Silesia). One patient was excluded from analysis because of a diagnosis of symptomatic lung cancer. In one patient the cancer diagnosis was missed due to false-negative result of screening [8]. At baseline, the positive result of screening was defined as the presence of a solid or part-solid nodule ≥ 5 mm, and ≥ 8 mm in the case of a nonsolid nodule, in line with the IELCAP protocol [2]. The sizes for nodules were computed based on the measurements performed in two transverse sections. Positive results were followed up with subsequent scans and different invasive procedures (*e.g.* bronchoscopy, endobronchial ultrasound-guided biopsy, transthoracic biopsy) aiming for lung cancer verification (true-positive). Other nodules confirmed in histopathological analyses as benign lesions were defined as false-positive results of screening [8]. In this analysis, we focused on the first-round results; the algorithm of the procedure is presented in Table 1.

To assess the effect of the Lung-RADS® protocol on the performance LDCT screening in the Silesian Pilot Study [8], the criteria of the screening protocol [3] were retrospectively applied to nodule-level data and compared with the primary IELCAP protocol-based data. The comparison included some imaging and invasive procedures performed within alternative screening protocols, sensitivity, and specificity of protocols. Sensitivity was the percentage of screenings with cancer present that were positive; specificity was the percentage of screenings with cancer absent that were negative. The comparison was limited to the results of the baseline LDCT scans.

Results

The Pilot Silesian Study database lists in total 1016 nodules with a diameter ≥ 3 mm detected in 265 persons during the baseline screening. In this set 110 solid, 46 part-solid, and 44 nonsolid nodules were classified as positive results according to the IELCAP protocol. When the Lung-RADS® protocol was applied, the number of positive screening results decreased to 73 solid, 19 part-solid, and 24 nonsolid nodules.

Table 1. Algorithm of the work-up procedures based on the IELCAP protocol

Detected lesion	Recommended LDCT interval or further work-up
SPN ≤ 5 mm	LDCT in 12 months
SPN 6–7 mm	LDCT in 6 months
SPN 8–14 mm solid or part-solid	LDCT in 3 months
SPN ≥ 15 mm	— CT-PET — Biopsy (CT- or US-guided TTNB, EBUS-TBNA, rEBUS-TBNA) — Suspected infectious lesion; antibiotic course; f/u LDCT in 1 month
Intrabronchial SPN	Bronchoscopy

LDCT negative result — further CT not required in the pilot study
LDCT positive result — one solid or partsolid nodule ≥ 5 mm or one nonsolid nodule ≥ 20 mm (annual screening with LDCT in 12 months)

Table 2. Diagnostic procedures with the IELCAP and Lung-RADS® protocols

	IELCAP protocol, n	Lung-RADS® protocol, n	Avoided positive screenings/procedures, n (%)
Number of positive screening results	200	116	84 (42.0)
Follow-up chest CT scans	58	28	30 (48.8)
Bronchoscopy	16	11	5 (31.2)
Endobronchial ultrasound	5	4	1 (20.0)
Transthoracic biopsy	8	7	1 (12.5)

Lung cancer was diagnosed in seven patients after the baseline screening. In one patient two independent, synchronous cancers were diagnosed (large-cell carcinoma and small-cell lung carcinoma). The malignant lesions had an average diameter of 20.25 mm. All were solid nodules. It the case of one person a 15 mm solid nodule was missed at baseline screening and detected in the subsequent scan (false negative result). A change in the scanning protocol from IELCP to Lung-RADS® did not result in changes in the number of true-positive cancer cases or missed (false negative) malignant lesions.

Screening based on the IELCAP protocol resulted in 200 positive results and based on Lung-RADS® in the 116 positives. Both screening protocols had the same sensitivity of 87.5%, and the Lung-RADS® protocol had higher specificity of 81.8% compared to 67.5% in IELCAP. The frequency of lung cancers among participants with a positive result diagnosed in the baseline LDCT scan (positive predictive value) was 7 of 200 (4.0%) [95% confidence interval (CI): 1.0%, 6.0%] for IELCAP and 7 of 116 (6.0%) (95% CI: 2.7%, 9.3%) for Lung-RADS®.

Each positive screening result indicated the necessity of follow-up with the use of noninvasive and/or invasive procedures aiming for further monitoring of detected nodules and diagnosis. Table 2 shows screening-resultant diagnostic procedures performed according to the IELCAP protocol and in the case of use of the Lung-RADS® protocol. The lower number of false positive screening results under the Lung-RADS® protocol allowed us to avoid some diagnostic procedures in comparison to IELCAP. Use of the Lung-RADS® criteria allowed us to reduce the number of noninvasive procedures by 48.8% and invasive procedures by 24.1%, compared to IELCAP-based screening at baseline. Avoidance of subsequent procedures concerned persons with nodules of the second category (13 noninvasive and two invasive procedures avoided) and category 3 (17 noninvasive and three invasive procedures avoided).

Discussion

In cases of malignant nodules, the early diagnosis of lung cancer could provide a safe and definitive solution. Understanding the clinical significance of numerous detected pulmonary nodules in population-level screening initiatives is an important challenge of their optimal management, reducing harm, and financial aspects.

The current analysis addressed the relevance of the nodule size on the performance of two lung cancer screening protocols. Screening based on the IELCAP protocol showed that the risk of malignancy in solid nodules < 5 mm diameter is ≤ 1% [4]. In the Lung-RADS® protocol, solid and part-solid nodules < 6 mm are indicated as benign appearance, with < 1% chance of malignancy and with follow-up after 12 months [5, 9]. Applying the Lung-RADS® protocol to the IELCAP-based screening results reduced the number of false-positive results with no decrease of sensitivity. It suggests better performance for Lung-RADS® than IELCAP as an element of LDCT screening. The previous study showed a similar effect on the false-positive result rate when Lung-RADS® criteria were applied to the results of the National Lung Screening Trial [8]. However, in contrast to the current analysis, sensitivity also decreased in that study, increasing the risk of false-negative results under the Lung-RADS® protocol [8]. All pulmonary nodules identified in the Silesian Pilot Study were large lesions categorised as 4B at baseline scans, with > 15% risk of cancer. There was a two-fold difference between the average diameter of malignant lesions identified in the National Lung Screening Trial and the Silesian Pilot Study (9.9 *vs*. 20.2 mm), which explains the lack of increase in the rate of false negative results in the current analysis. There is an urgent need to adapt the European and American guidelines and recommendations to Polish conditions and consider the possibility of implementation of a lung cancer screening program [10].

Use of the Lung-RADS® protocol may significantly reduce the burden of procedures. In most persons with nodules of categories 2 and 3 it was possible to avoid subsequent chest computed tomography exams and bronchoscopies. Overall it was possible to avoid almost half of the noninvasive and every fourth invasive procedure/s after the baseline screening. Reducing the number of unnecessary follow-ups is important, especially in countries with many potential candidates

for the screening program and its associated significant financial effort.

It is important to note the limitations of the analysis. The major limitation is that the analysis was retrospective and performed on a relatively small sample size compared to other screening prospective studies [1]. There is a potential measurement inaccuracy leading to variability in the size of nodules. The analysis was limited to the baseline screening; thus, conclusions should be limited to the initial screening. It is not only nodule size that drives its management but also the volume and growth rate, which can be measured in a series of subsequent scans [11].

Adopting the Lung-RADS® classification system may reduce harm and improve the efficiency of lung cancer screening programs. The initial observation of the advantages of the Lung-RADS® protocol should be confirmed in a prospective setting.

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Conflict of interest

None declared.

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REVIEW ARTICLE

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Summary of immunotherapy efficacy ordered in accordance with drug reimbursement program in melanoma patients

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ABSTRACT

Nivolumab and pembrolizumab are monoclonal antibodies of the IgG4 class, which target the cell death receptor (PD-1) found on T cells. The binding of the anti-PD-1 drug to the receptor therefore prevents the inhibition of these T cells and increases the immune response against melanoma cells. Pembrolizumab and nivolumab monotherapy has similar efficacy, including PFS and OS. Nivolumab and pembrolizumab immunotherapy are effective regardless of the *BRAF* mutation status. Currently, the choice between nivolumab and pembrolizumab is primarily dependent on to the frequency of infusions (every 3 weeks for pembrolizumab *vs.* every 2 weeks for nivolumab or every 6 weeks *vs.* every 4 weeks). Based on the available data, it can be concluded that autoimmune disease is not an absolute contraindication to the use of immunotherapy, but close clinical monitoring of these patients and specialist consultations (e.g. rheumatologist, dermatologist) must be provided. Patients with severe autoimmune disease who are treated with biologicals or have a history of life-threatening autoimmune disease complications (e.g. severe Crohn's disease) should not be qualified for immunotherapy, as opposed to patients with minimally symptomatic autoimmune disease (e.g., mild dermal psoriasis).

Key words: melanoma, immunotherapy, nivolumab, pembrolizumab

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Introduction

The relatively recent registration of immunotherapy initiated a significant change in treating patients diagnosed with advanced melanoma. Before 2011 patients with melanoma in the dissemination stage were treated palliatively by chemotherapy (dacarbazine), and this treatment did not prolong overall survival. In 2019, because of the registration and refunding of immunotherapy, patients with melanoma could obtain long-term responses and overall survival (OS), including complete responses (CR) to treatment. The basis of immunotherapy in patients with advanced melanoma is antibodies directed against the programmed death cell receptor-1 (PD-1) — pembrolizumab and nivolumab, used in monotherapy or in combination therapy with antibodies directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) — ipilimumab. Ipilimumab is an antibody registered in 2011 directed against the CTLA-4 protein, which was the first to give a significant prolongation of overall survival with a simultaneous low percentage of responses (approx. 10%). In prospective clinical trials the advantage of PD-1 inhibitors such as pembrolizumab and nivolumab over anti-CTLA4 antibodies was demonstrated in first-line melanoma treatment in the form of a greater chance of obtaining objective responses (overall response rate; ORR) to treatment and longer progression-free survival (PFS), as well as longer overall survival. Nivolumab and pembrolizumab are monoclonal antibodies of the IgG4 class, which attach to the cell death receptor PD-1 on

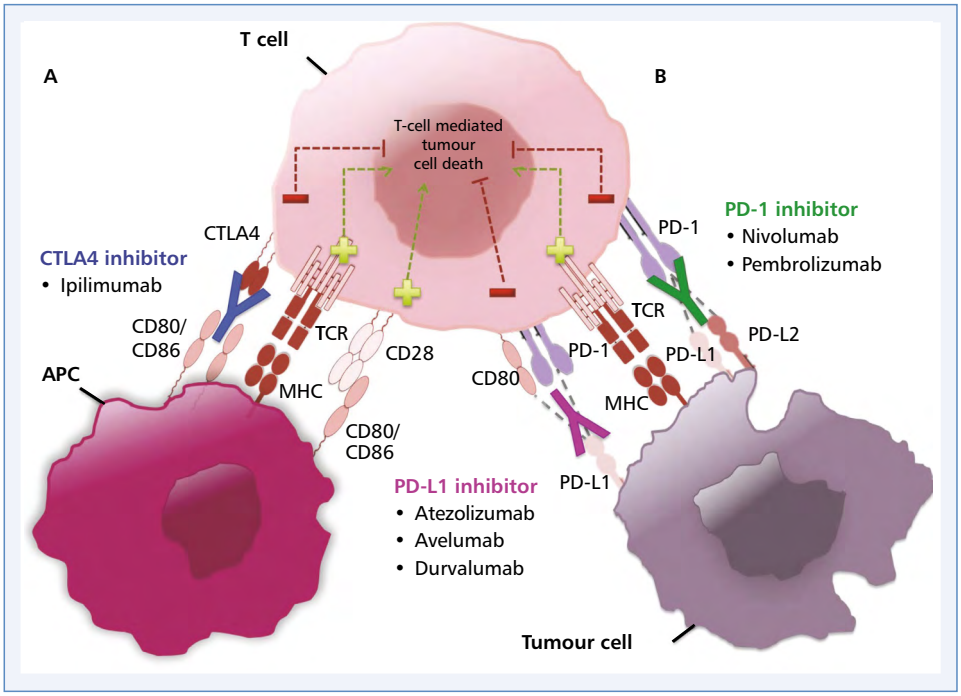

Figure 1. Mechanism of immunotherapy action [1]. In the first stage of the immune response, naive T cells in lymphatic organs (e.g. lymph nodes) are presented with antigens specific for the neoplasm, which causes the differentiation of naive T cells into effector T cells (e.g. Treg, cytotoxic T cells, and helper T cells). This process is intensified by a co-stimulating signal from the CD28 receptor from CD80/86. CD28 activation is inhibited in the presence of the CTLA-4 receptor, which has a much higher affinity for CD80/86 ligands. Antibodies blocking CTLA-4 prevent this inhibition and stimulate the maturation of effector T cells capable of an anti-neoplasm response. Moreover, anti-CTLA-4 antibodies can be involved in inhibition of Treg cells in the tumour microenvironment. In the effector phase of the immune response cytotoxic cells in the tumour microenvironment eliminate tumour cells; however, their activity is suppressed by interactions between the PD-1 receptor on T cells and PD-L1 or to a smaller extent PD-L2 on the surface of tumour cells and macrophages in the tumour. Inhibition of the PD-1/PD-L1 pathway enables T cell activation and restores T cell response against neoplasm cells

CD4+, CD8+ T lymphocytes, B lymphocytes, and myeloid cells and prevent the death of immune system cells. The binding of the anti-PD-1 drug to the receptor prevents the inhibition of the functions of these cells and strengthens the immune response to neoplastic cells (Figure 1) [2].

Treating patients without the *BRAF* mutation

Currently, melanoma patients without a mutation in the *BRAF* gene (*BRAF-WT*) in the frame of the drug program for treatment of cutaneous and mucosal melanoma (ICD-10 C43) can be treated in the first line by nivolumab or pembrolizumab in monotherapy, and the choice of the drug is left to the decision of the attending physician after a discussion with the patient (Figure 2). Both drugs were registered on the basis of phase III trials [4, 5].

The registration trial evaluating the effectiveness of first-line treatment with nivolumab in monotherapy in patients with a diagnosis of locally advanced non-resectable or metastatic melanoma *BRAF-WT* was the CheckMate066 trial (NCT01721772). The trial included 418 patients who were randomly assigned in a ratio of 1:1 to treatment with nivolumab administered at a dose of 3 mg/kg body mass every two weeks or the branch with dacarbazine administered at a dose of 1000 mg/m^2 body surface, and the treatment was continued until disease progression or unacceptable toxicity. In the nivolumab group the median age of the patients was 64 years (range 18–86 years) and 57.6% were men; for dacarbazine the median age was 66 years (range 25–87 years) and 60.1% were men. The median progression-free survival (PFS) was 5.1 months for nivolumab treatment and 2.2 months for dacarbazine treatment (HR = 0.43; 95% CI: 0.34–0.56; P < 0.001). The ORR percentage was 40% for persons treated with nivolumab and 13.9% for those treated with dacarbazine [6]. After more than 38 months

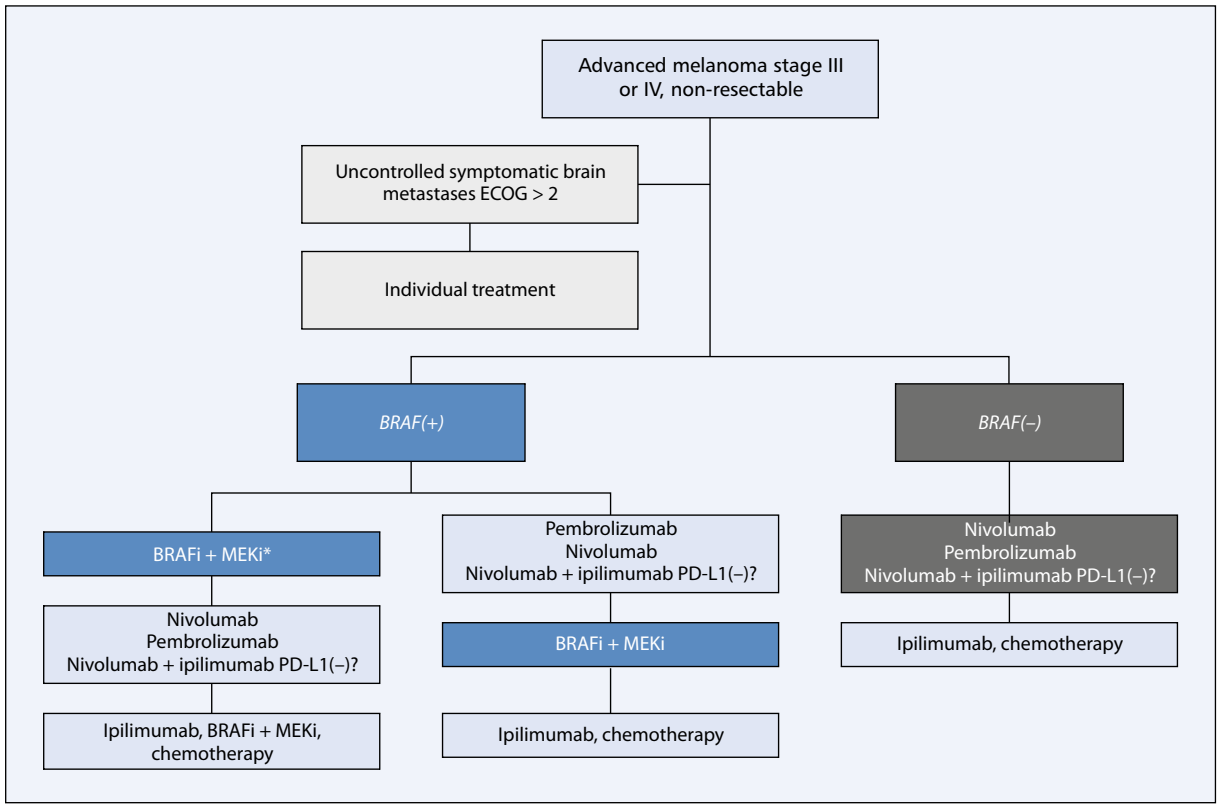

Figure 2. Scheme of systemic melanoma treatment including immunotherapy [3]. **?** — indication registered but not reimbursed; *— dabrafenib + trametinib, vemurafenib + cobimetinib or encorafenib + binimetinib

of observation in the group treated with nivolumab three-year OS indices were 51.2% (95% CI, 44.1–57.9) and in the group treated with dacarbazine — 21.6% (95% CI, 16.1–27.6). The median OS was 37.5 months (95% CI, 25.5 months–not reached) in the nivolumab group and 11.2 months (95% CI, 9.6–13.0 months) in the group treated with dacarbazine (risk coefficient 0.46; 95% CI, 0.36–0.59; $P < 0.001$) (Figure 3). At the moment of data analysis 63.8% (134 of 210) of patients in the nivolumab group had disease progression or died, in comparison to 82.7% (172 of 208) of patients in the dacarbazine group, and three-year PFS indices were 32.2% (95% CI, 25.6–39.0) and 2.9% (95% CI, 0.7–8.1), respectively. Subgroup analysis indicated that in patients with PD-L1 expression of at least 5% the median OS was not reached (95% CI, 4.4–NR) in the nivolumab treatment group and was 9.7 months (95% CI, 6.7––13.5 months) in the dacarbazine treatment group. In patients with PD-L1 expression lower than 5% the median OS during nivolumab treatment was 28.2 months (95% CI, 18.2–38.5 months) and 11.6 months (95% CI, 9.3–13.0 months) for patients treated with dacarbazine. Similarly, regardless of PD-L1 expression, patients in the group treated with nivolumab had longer progression-free survival in comparison to patients from the group treated with dacarbazine — CR and partial response (PR) were noted in 19.0% (40 of 210) and 23.8% (50 of 210) of patients, respectively, in the group treated with nivolumab in comparison to 1.4% (3 of 208) and 13.0% (27 of 208) of patients in the group treated with dacarbazine. Treatment-related undesirable effects of the third/fourth degree occurred in 15.0% (31 of 206) of patients treated with nivolumab and in 17.6% (36 of 205) of patients treated with dacarbazine, and no deaths due to the toxicity of either of the drugs were observed [7].

The first trial evaluating the treatment effectiveness of pembrolizumab in monotherapy in first-line treatment in patients with nonresectable or metastatic melanoma was the KEYNOTE-001 trial, in which 655 patients were randomised into melanoma cohorts; 151 of them had not been treated previously, and 496 had been treated (205 received one previous therapy, 178 received two previous therapies, 113 received three or more previous therapies). At the moment of data analysis 63% (n = 412) of all patients had died and 54% (n = 81) of all previously untreated patients had died. In a three-year analysis in previously untreated patients the median OS was 31 months (95% CI, 24–NR), with a 12-month survival index of 73% (95% CI, 65–79) and a 24 month survival index of 60% (95%

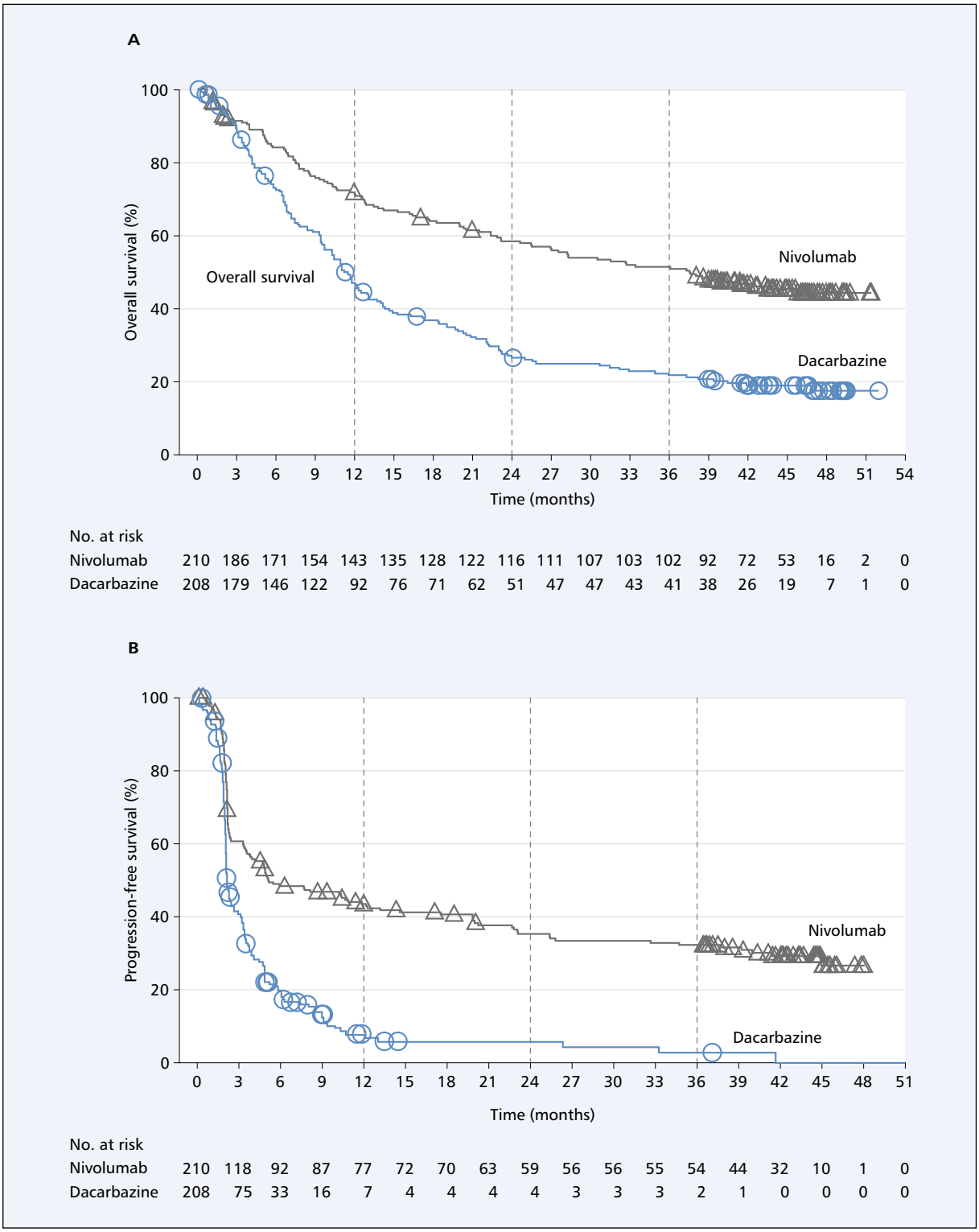

Figure 3. Long-term overall survival (**A**) and time to disease progression (**B**) in melanoma patients without the *BRAF* gene mutations treated with nivolumab in first-line treatment [7]

CI, 51–68) [8]. The estimated index of five-year OS was 34% in the whole patient cohort and 41% in previously untreated patients. Median OS was 23.8 months (95% CI, 20.2–30.4) in the whole cohort and 38.6 months (95% CI, 27.2–NR) in previously untreated patients (Fig. 1A and B). The five-year estimated PFS index was 21%

and 29%, respectively. Median PFS was 8.3 months (95% CI, 5.8–11.1) in the whole cohort and 16.9 months (95% CI, 9.3–35.5) in previously untreated patients. In those treated with pembrolizumab as first-line treatment CR was reached by 38 patients (25%), 40 (27%) reached PR, and 30 (20%) had stable disease (SD), and finally 32 patients (21%) had progressive disease (PD). Median time to response in patients treated in the first line was 2.8 months (range: 2.5–32.0), and the median time of maintained response was not attained (range: 1.3+ to 60.8+ months). Among 38 patients who reached CR, median time to response was 2.8 months (range: 2.5–8.3), and median time of response duration was also not attained (range: 6.0+ to 60.8+ months). The response was still present in 35 patients (92%) at the moment of data analysis. Among 40 patients who attained PR, median time to response was 2.8 months (range: 2.5–32.0), and median time of response duration was also not attained (range: 1.3+ to 51.4+ months), and in the 29 previously untreated patients (73%) who reached PR at the moment of data analysis the response was still ongoing. In this trial in the whole analysed population 156 (24%) patients had a diagnosis of *BRAF*+ melanoma [9].

The second trial in which first-line pembrolizumab treatment was given to patients with melanoma in the dissemination stage was the KEYNOTE-006 trial. Pembrolizumab and ipilimumab treatments were compared. Among patients who received pembrolizumab as first-line treatment the median OS was 38.7 months *vs*. 17.1 months (HR = 0.73, p = 0.0036) for those treated with ipilimumab, and median PFS was 11.6 months *vs*. 3.7 months (HR = 0.54, P < 0.0001). The patients who were not treated in the first line were those who had previously received chemotherapy (14% for pembrolizumab and 10% for ipilimumab), BRAF or MEK inhibitors (17% and 20%), or immunotherapy (3% and 4%). In patients receiving second-line treatment with pembrolizumab the median OS was 23.5 months in comparison with 13.6 months (HR = 0.75, P = 0.036) for ipilimumab treatment [10]. In the previously untreated population, the percentage of ORR was 39.4% (95% CI, 34.4–44.6%) for pembrolizumab treatment in comparison with 13.3% (95% CI. 8.7–19.1%) for ipilimumab. Median time to response was 12.1 weeks (range 3.7––48.1 weeks) and 12.6 weeks (range 11.4–42.4 weeks), respectively, and the median time of response duration was not attained in any of the groups (range: 7.7–99.1+ weeks with pembrolizumab and 4.7+ to 95.9+ weeks with ipilimumab). When pembrolizumab was used the best complete response was CR in 52 patients (14.1%), and PR occurred in 93 (25.3%); 40 (10.9%) had SD. For ipilimumab CR was obtained in seven patients (3.9%), PR in 17 (9.4%), and 30 (16.6%) had SD [11]. In the KEYNOTE-006 trial in patients with *BRAF-WT* melanoma median OS was 28.1 months for pembrolizumab treatment *vs.* 13.9 months for ipilimumab treatment (HR = 0.73, P = 0.0048) (Figure 4). In patients with the *BRAF* gene V600E mutation or a *BRAF* V600K mutation previously treated with BRAF or MEK inhibitors median OS was 20.4 months for pembrolizumab treatment in comparison with 11.9 months for ipilimumab treatment (HR = 0.71, p = 0.054). In patients with melanomas with the *BRAF* V600E or V600K mutation not treated previously with BRAF or MEK inhibitors (patients with initial normal levels of lactate dehydrogenase) median OS was not attained during pembrolizumab treatment in comparison with 26.2 months during ipilimumab treatment (HR = 0.70, P = 0. 065) [10].

Comparison of nivolumab and pembrolizumab use

Monotherapy with pembrolizumab or nivolumab has similar effectiveness, including the range of PFS and OS (Figure 5). Currently the choice between nivolumab and pembrolizumab also concerns, above all, the frequency of infusions (every three weeks for pembrolizumab in comparison with every two weeks in the case of nivolumab or every six, as compared to every four weeks). An American analysis based on the evaluation of the Flatiron Health Inc. Database encompassing data from over 280 regional oncological centres, seven main academic research centres and 15 leading oncological companies described 888 patients with advanced melanoma, of whom in the first line 486 patients were treated with pembrolizumab and 402 patients with nivolumab. In 58% patients treated with nivolumab a constant 240 mg dose was administered every two weeks, and in the 38% of patients treated with pembrolizumab — 200 mg every three weeks, the remaining patients were treated using doses calculated per kilogram body weight. Median OS for patients treated with pembrolizumab was 22.6 months and for those treated with nivolumab — 23.9 months (P = 0.91), and no differences were found in survival between patients treated with pembrolizumab and nivolumab (HR 1.10; 95% CI, 0.87–1.39). Similar results were obtained in clinical practice within the framework of drug programs of melanoma treatment in the Centre for Oncology in Warsaw (Figure 6). Because of the lack of significant differences in the effectiveness of nivolumab in comparison to pembrolizumab an additional factor supporting the decision as to the choice of drug can be the toxicity profile of the anti-PD-1 drug, which is different depending on the drug and should be considered in respect to the accompanying diseases and the patient's age [13].

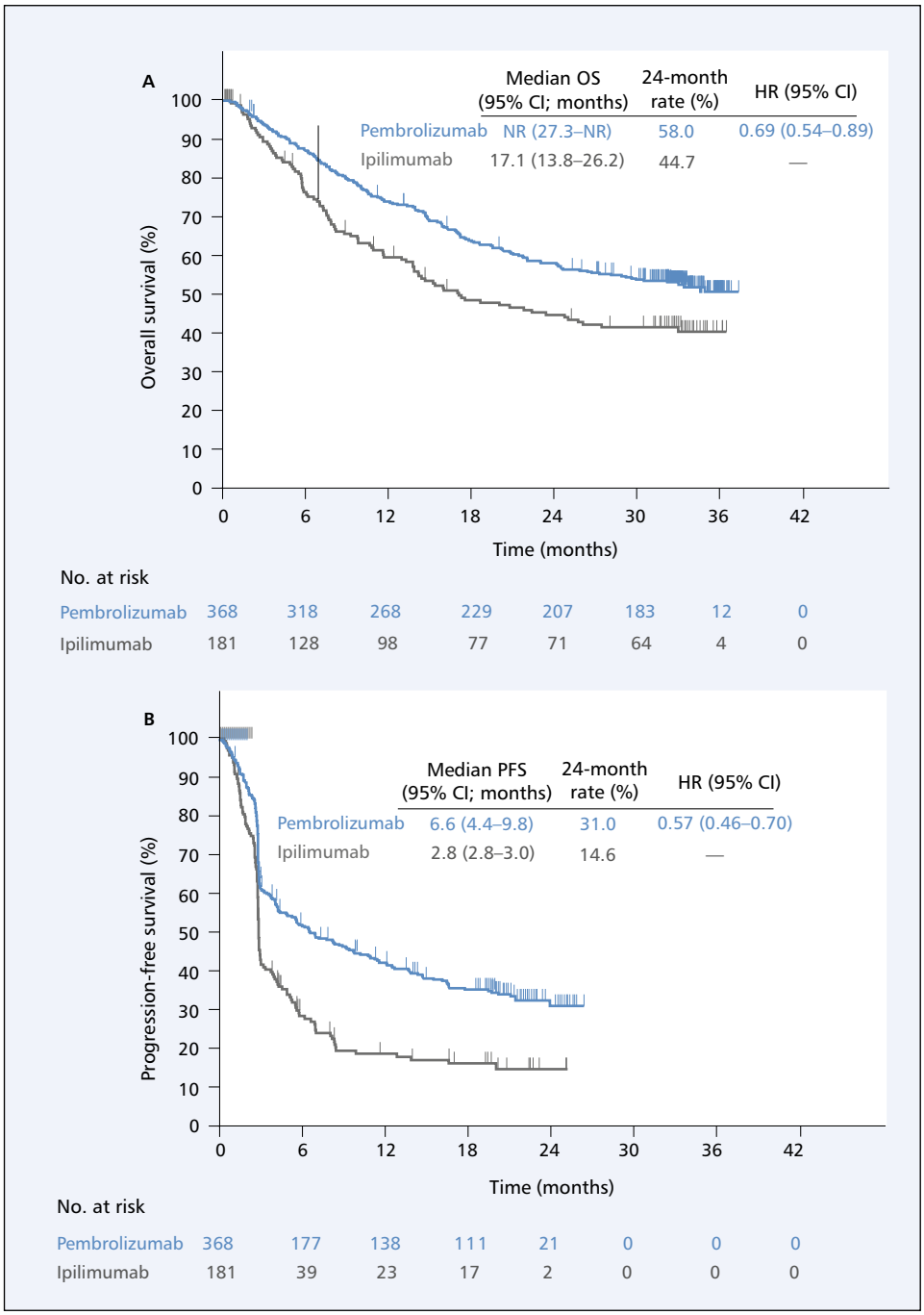

Figure 4. Long-term overall survival (**A**) and time to disease progression (**B**) in melanoma patients treated with pembrolizumab in first-line treatment [11]. NR — not reached

Treatment of patients with the *BRAF* mutation

Immunotherapy with anti-PD-1 antibodies (nivolumab, pembrolizumab) is effective regardless of the *BRAF* mutation status [14]. Analysis of treatment of patients included in the CA209-003 (NCT00730639), CA209--038 (NCT01621490), CA209-004 (NCT01024231), and CA209-037 (CheckMate037, NCT01721746) trials showed that for nivolumab treatment the median time of OR duration is 14.8 months (95% CI, 11.1–24.0 months) for melanoma patients without the *BRAF* gene mutation (*BRAF-WT*) and 11.2 months (95% CI, 7.3–22.9 months) for melanoma patients with *BRAF* gene mutations (*BRAF+*). ORR was 34.6% for patients with B*RAF-WT* (75 responses for 217 cases)

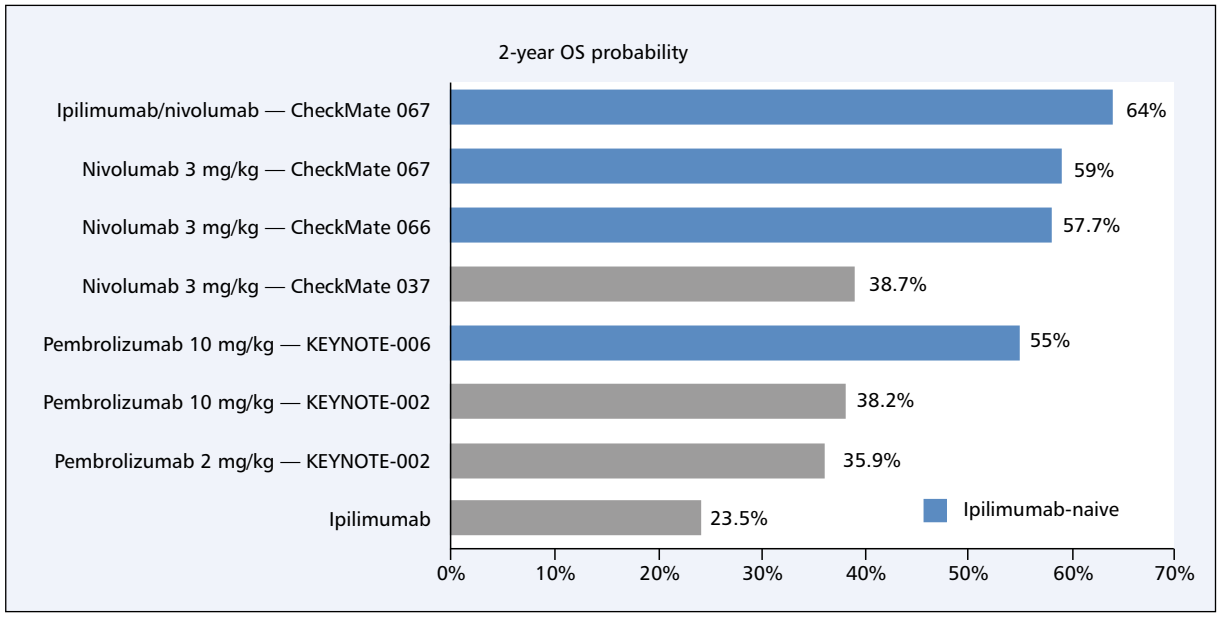

Figure 5. Overall survival index after two years of anti-PD-1 therapy in advanced sarcoma [12]

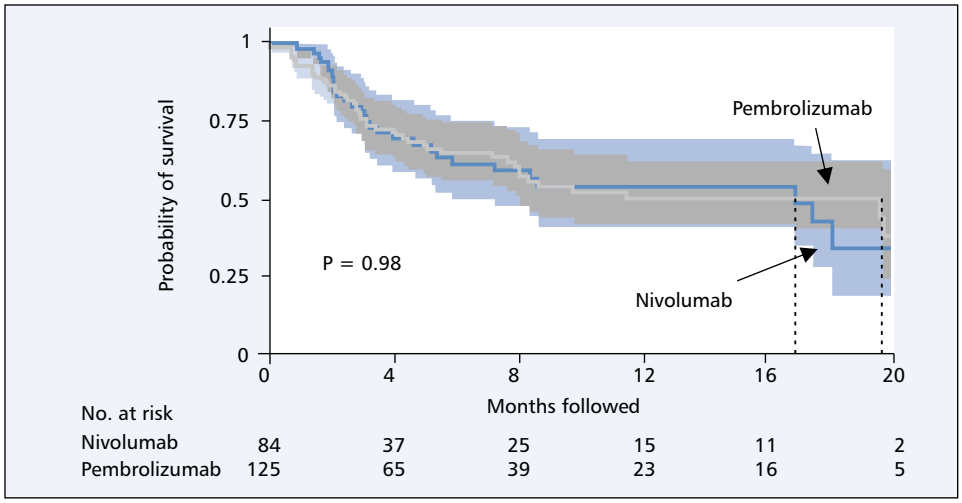

Figure 6. Overall survival time during nivolumab and pembrolizumab treatment (own data)

and 29.7% for patients with *BRAF+* (22 responses for 74 cases). Median time of OR duration was similar in patients with B*RAF-WT* (14.8 months; 95% CI, 11.1–24.0) and *BRAF+* (11.1 months; 95% CI, 7.3–22.9) [14]. In a more recent trial, CheckMate 067, also evaluating combined immunotherapy, it was shown that in the first line of treatment of patients with *BRAF+* melanoma after 28 months of observation median OS was not attained in the group treated with nivolumab with ipilimumab nor in the group treated with nivolumab and was 24.6 months in the ipilimumab group (95% CI, 17.9–33.0). In this group of patients with *BRAF+* melanoma the two-year overall survival OS was 71% for the combination, 62% for nivolumab, and 51% for ipilimumab [15]. The general indirect comparison of the effectiveness of BRAFi/MEKi and checkpoint inhibitors in patients with *BRAF+* melanoma indicates the superiority of molecularly directed therapies during the first 5–6 months, and the superiority of anti-PD-1 treatment or together with CTLA-4 in successive months of treatment. The first meta-analysis published in 2017 suggests that BRAFi/MEKi treatment is the most effective in the scope of improving OS, PFS, and ORR in patients with *BRAF+* melanoma, and is superior to immunotherapy in this area [16]. In turn, a Cochrane analysis indicated the superiority of immunotherapy in the scope of treat-

ment safety, and the superiority of BRAFi/MEKi in the scope of prolonging PFS [17]. The most recent analysis only comparing immunotherapy with a combination of nivolumab and ipilimumab *vs*. BRAFi/MEKi therapy indicated a statistically significant advantage in the scope of OS for nivolumab and ipilimumab in comparison with both schemes of BRAF and MEK inhibitors. For therapy a comparison of nivolumab + ipilimumab versus dabrafenib + trametinib HR (95% CI) was calculated as 0.64 (0.46, 0.89) and for nivolumab + ipilimumab *versus* vemurafenib + cobimetinib treatment — 0.56 (0.36, 0.89) [18]. However, so far, no randomised clinical trial comparing BRAFi/MEKi (dabrafenib + trametinib, vemurafenib + cobimetinib or enkorafenib+binimetinib) and immunotherapy (nivolumab or pembrolizumab) has been published, which does not allow the evaluation of optimal first-line treatment for patients with *BRAF*+ melanoma.

The optimal sequence of treatment with BRAF and MEK kinase inhibitors (BRAFi/MEKi) and immunotherapy is not defined at present. So far, there are no available prospective data from randomised trials allowing us to determine the best sequence of treating patients with *BRAF*+ melanoma. In particular, there are no prospective data concerning sequential treatment in patients with poor prognostic factors. The currently published joint analysis of phase II and III trials indicated that in the case of nivolumab treatment neither earlier therapy with BRAFi nor earlier treatment with ipilimumab have an effect on ORR. In this analysis ORR was 33.1% in *BRAF*+ patients without prior BRAFi treatment and 24.5% in patients who had previously received BRAFi. However, the direct interpretation of results is difficult because in patients treated with nivolumab earlier therapy with a BRAF inhibitor was applied in 71.7% (76) of *BRAF*+ patients, but in 85.8% (91) also more than two schemes of earlier treatment had been applied, including chemotherapy and ipilimumab according to inclusion criteria for the CheckMate 003, CheckMate 004, CheckMate 037, and CheckMate 038 trials [14].

The oldest analyses, because of the time of drug registration, evaluated the application of BRAFi/MEKi after ipilimumab. In the analysis by Ackerman et al. 274 patients with advanced melanoma with a *BRAF* mutation were evaluated, and the percentages of ORR, PFS, and OS were compared among patients who received immunotherapy (including high doses of interleukin 2, nivolumab, ipilimumab, or adoptive cell therapy) before directed therapy (encompassing vemurafenib in monotherapy, dabrafenib in monotherapy, and dabrafenib together with trametinib). In BRAFi treatment — 117 received vemurafenib, 99 — dabrafenib, and 58 — dabrafenib and trametinib. In this analysis RR, median PFS and OS for second-line BRAFi treatment (after immunotherapy with ipilimumab) was 57%, 6.7 months (n = 32, 95% CI, 4.3–9.1 months), and 19.6 months (95% CI, 10.0–NR months), respectively. At the same time, for first-line use of BRAFi (n = 242) these data were 66% RR, 5.6 months PFS (95% CI, 4.7–6.8 months), and 13.4 months OS (95% CI, 10.1–177.0 months). In these patients the response to targeted therapy was similar whether it was given before or after immunotherapy, but ORR and survival for the group treated with ipilimumab were better if it was used before targeted therapy. On the basis of such results the authors of the analysis concluded that the use of immunotherapy with ipilimumab as first-line treatment does not appear to negatively affect the response to BRAFi therapy [19]. Similarly, in the analysis by Ascierto et al. patients who received ipilimumab before targeted therapy had better OS in comparison with patients treated by targeted therapy and then ipilimumab [20]. On the basis of these two trials it began to be suggested that in the case of sequential treatment immunotherapy should be used first. Newer analyses also confirmed that ORR indices are lower in the case of ipilimumab therapy after progression to BRAFi; therefore, it was suggested that administering immunotherapy in the first line may be the best mode of action [21].

Current analyses are evaluating the use of BRAFi/MEKi after anti-PD1 therapy. In the analysis of Johnson et al. patients who received in the first line anti-PD-1 therapy (n = 56) were compared with those who were first treated with BRAFi/MEKi (n = 58). These two groups of patients had different PFS in second-line treatment, but median OS did not differ significantly between the groups (27.5 *vs*. 40.3 months, P = 0.71). Patients with progression on anti-PD-1 treatment had shorter survival after initiation of second-line BRAFi/MEKi therapy with as median PFS of five months and median OS of 10.6 months. The ORR index of anti-PD-1 therapy seemed to be slightly higher in the group not previously treated with BRAFi (first anti-PD-1) (41% *vs.* 25%) [19]. The most recent analyses have indicated that BRAFi/MEKi given after anti-PD-1 therapy is less effective, and it was suggested that there could be a common mechanism of resistance to the two treatment methods [22].

Summing up, it is now known that both BRAFi/MEKi therapy as well as immunotherapy (anti-PD-1 monotherapy) are effective methods of treating patients with *BRAF*+ melanoma in the dissemination stage, and long-term responses are observed in both subgroups of patients, regardless of earlier therapies. In patients with a good performance status and proper organ function, anti-PD-1 treatment can be considered regardless of the status of the *BRAF* mutation. However, clinicians should maintain particular care in qualifying patients with an initially unfavourable prognosis for treatment. The

results of the analysis of registration trials (nivolumab, pembrolizumab) cannot be directly transferred to patients who do not fulfil the qualification criteria for these trials, for instance patients with a poor performance status, because the percentages of responses to immunotherapy may not be similar in patients with *BRAF*-WT and *BRAF*+ melanomas in patients with high LDH, metastases to the CNS, or a large tumour mass and metastases to many parenchymal organs. Moreover, the optimal sequence of BRAFi/MEKi therapy and immunotherapy in treating patients with melanoma is still under discussion and is the subject of evaluation of four ongoing clinical trials (SECOMBIT, EBIN, i.e. EORTC 1612-MG and ECOG-ACRIN SWITCH, i.e. EA6134 and DREAMseq). It should, however, be pointed out that all these ongoing trials encompass in one arm combined immunotherapy (anti-PD-1 and anti-CTLA-4), whereas SECOMBIT and EBIN analyse the combination of encorafenib with binimetinib, and these strategies are currently not available in Poland in the scope of drug programs. It seems that the ongoing trials will determine the effect of the sequence of therapy directed against BRAF and the blocking of PD-1 and/or CTLA-4 on the results of treatment and survival of patients with melanoma in the dissemination stage. Clinical trials encompassing blocking PD-1, and also new trials of combinations of various immunotherapies or the analysis of combinations of targeted therapies may be considered as the first line of therapy options for all patients with advanced melanoma [23].

Immunotherapy and immunosuppression and autoimmune diseases

At present the meta-analysis of data or diagnostic-therapeutic recommendations concerning the safety and effectiveness of anti-PD-1 and anti-CTLA-4 antibodies in patients with previously existing autoimmune diseases are not available. A population epidemiological analysis performed in the USA indicated that this is a significant clinical problem concerning as many as one in five patients. The occurrence of prior autoimmune diseases in melanoma patients was calculated. Among 12,028 patients with newly diagnosed melanoma in the dissemination stage the frequency of occurrence of autoimmune diseases rose from 17.1% in 2004 to 28.3% in 2014 [24]. A similar frequency of autoimmune diseases can be expected in the Polish population among patients who are to start treatment in the Drug Program of treating melanoma by immunotherapy [25, 26]. Data available so far indicate the possibility of using systemic treatment of melanoma by immunotherapy in selected patients from this group.

In a multicentre trial directed by Melanoma Institute Australia and the University of Sydney in patients treated using anti-PD1 immunotherapy for melanoma in the dissemination stage with an existing autoimmune disease (N = 52) the percentage of responses was 33%. During anti-PD-1 immunotherapy exacerbations occurred in patients with rheumatological problems (14/27), psoriasis (3/8), Graves' disease (1/4), and immunological thrombocytopaenic purpura (2/2). Moreover, 20 (38%) patients had autoimmune disease exacerbations that required immunosuppression; these were patients with rheumatoid arthritis (7/13), rheumatic polymyalgia (3/3), Sjogren's syndrome (2/2), immunological thrombocytopenic purpura (2/2), and patients with psoriasis (3/8). Only two (4%) patients stopped treatment because of exacerbation of their autoimmune disease, and no deaths linked to treatment were noted. Clinical recurrence or an increase of previous symptoms were described (e.g. joint pain in patients with rheumatoid arthritis, increased skin symptoms in psoriasis patients), but not the occurrence of new disease symptoms (e.g. new lung symptoms in patients with rheumatoid arthritis). Exacerbations were more common in persons with active symptoms at the moment of ipilimumab treatment initiation (9/15, 60%) than in patients with clinically inactive disease (11/37, 30%) (P = 0.039). A tendency was also described of an increase in the number of exacerbations in persons receiving immunosuppressive drugs at the time of initiation of systemic melanoma treatment (10/20, 50%) in comparison with patients not requiring the administration of immunosuppressive drugs (10/32, 31%) (P > 0.05) at the time of qualification for immunotherapy. It is worth noting, however, that two of seven patients taking steroid drugs at the beginning of the treatment obtained an objective response, but none of the patients receiving other immunosuppressive drugs (including methotrexate); also, no objective responses were noted in patients who were taking steroids in combination with another immunosuppressive drug, which appears to be linked to the immunosuppressive mechanism of steroids and methotrexate (Figure 7), which prevent lymphocyte activation induced by immunotherapy (Figure 1) [30]. Analogous data have been published for ipilimumab treatment. Thirty patients were evaluated; they received ipilimumab and concurrently: six had rheumatoid arthritis, five — psoriasis, six — inflammatory bowel disease, two — systemic lupus erythematosus, two — multiple sclerosis, two — autoimmunological thyroid inflammation, and seven had other diseases. In the analysed cohort 13 patients (43%) were receiving immunosuppressive treatment at the moment of initiating ipilimumab treatment, most commonly with small doses of prednisone or hydroxychloroquine. During ipilimumab treatment eight patients (27%) had exacerbation of their immunological disease requiring

systemic treatment, but all were sufficiently controlled by corticosteroids. Undesirable effects dependent on the immunological mechanisms in degree 3 to 5 occurred in patients (33%) and were reversible after using corticosteroids or therapy with infliximab in two cases, but one patient with a psoriasis diagnosis died because of colon inflammation. At the same time in 15 patients (50%) neither exacerbation of the autoimmune disease nor irAE were observed. In six patients (20%) objective responses were described, including one with a persistent CR [31]. Finally, the most recent research has shown that it is still unclear whether the number of life-threatening and fatal complications is small in patients with autoimmune diseases treated with immunotherapy because one meta-analysis (of patients with all types of neoplasms) indicated that fatal toxic action was observed in three out of 123 patients [32].

Currently, trial NCT03140137 is ongoing (112 patients are to be analysed) to determine the tolerance of immunological checkpoint inhibitors in patients with prior autoimmune diseases. Trial NCT03816345 (AIM-NIVO) will evaluate the safety of using nivolumab in patients

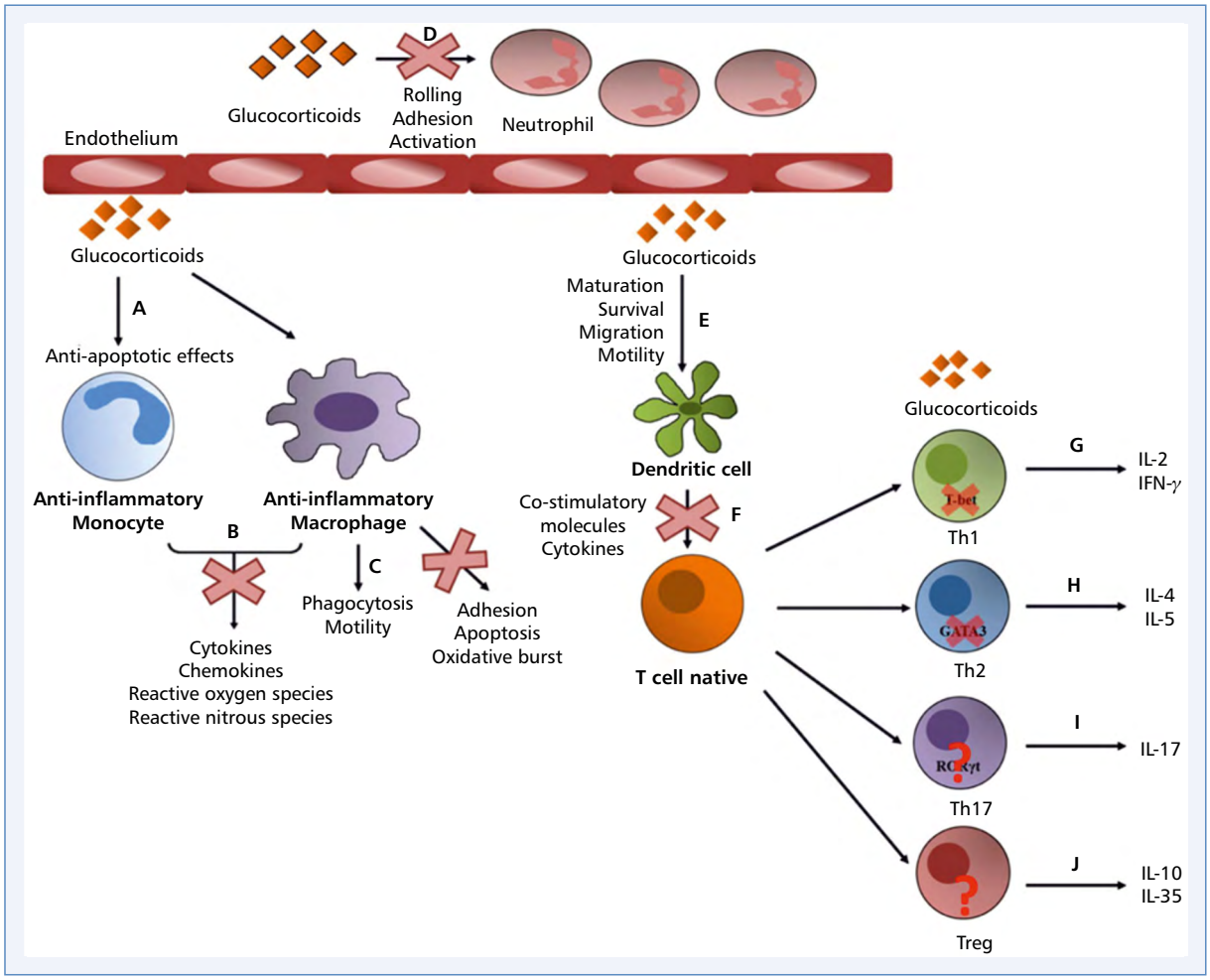

Figure 7A. Immunological basis for the lack of effects of immunotherapy in patients treated by immunosuppression — effect of steroid drugs on cells of the immune system [27]. Glucocorticoids act on almost all types of cells of the immune system and promote an anti-inflammatory state in both monocytes and macrophages. They prevent monocyte apoptosis (**A**) and inhibit the liberation of proinflammatory mediators by monocytes and macrophages (**B**). In macrophages they promote phagocytosis and mobility, inhibiting adhesion, apoptosis, and oxygen burst (**C**). They also act on neutrophil function by inhibiting their movement, adhesion to the substrate, and activation (**D**). Steroids also affect dendritic cell function, promoting their maturation, survival, migration, and mobility (**E**), and at the same time affecting their ability to activate T cells by inhibiting proinflammatory molecule production (**F**). Steroids also act on T helper (Th) cells, including the decrease of transcriptional activity of Th1 cells, and inhibit the production of proinflammatory molecules such as IL-2 and IFNγ (**G**). They also suppress the activity of the GATA3 gene in Th2 cells, inhibiting IL-4 and IL-5 expression (**H**). The action of steroids on Th17 cells (**I**) and regulatory T lymphocytes in not well understood (**J**)

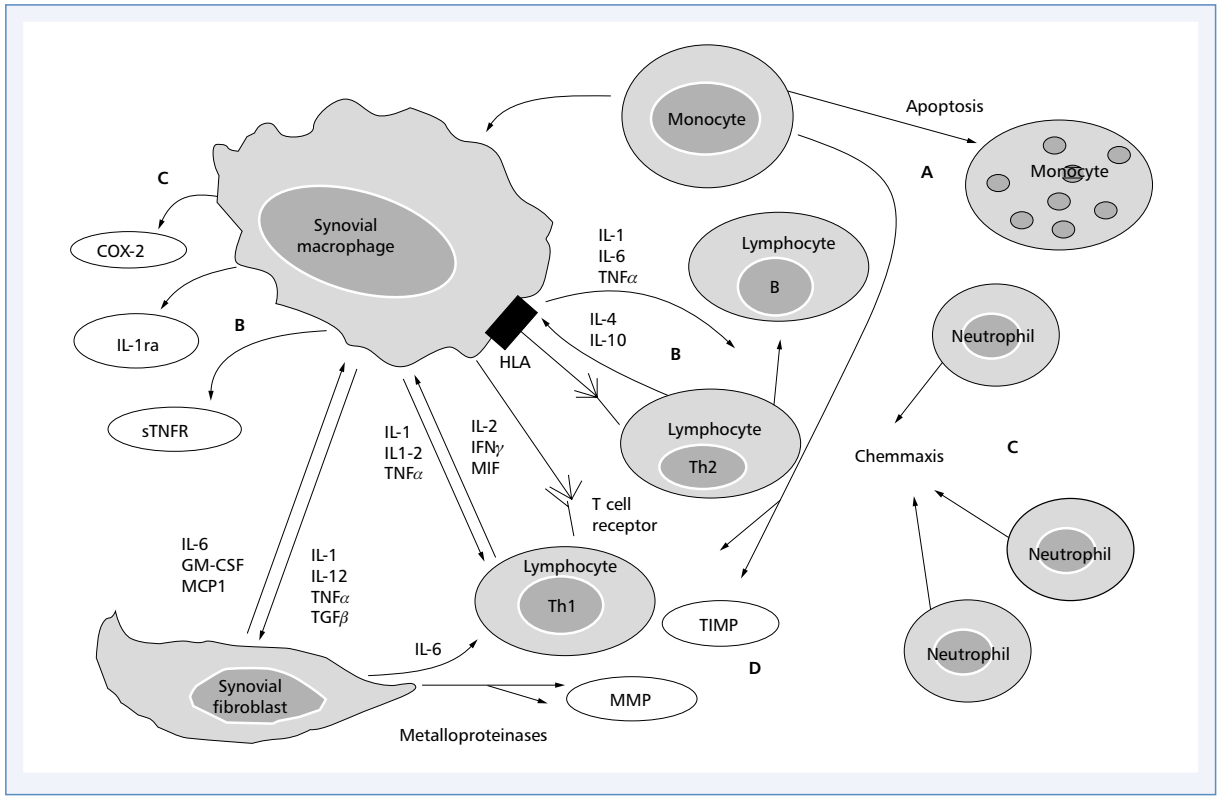

Figure 7B. Immunological basis for the lack of effects of immunotherapy in patients treated by immunosuppression — effect of methotrexate on cells of the immune system [28]. (**A**) MTX inhibits monocyte growth and increases their apoptosis. (**B**) MTX decreases IL1 and IL6 secretion and increases IL-1ra production. At the same time, MTX increases the expression of the IL-4 and IL-10 genes and decreases the expression of pro-inflammatory cytokine genes Th1 (IL-2 and IFNγ). (**C**) MTX inhibits COX-2 synthesis and neutrophil chemotaxis, which is dependent on it. (**D**) MTX indirectly inhibits (via cytokine modulation) metalloproteinase production. MTX — methotrexate; IL-1ra — interleukin-1 receptor antagonist; IFNγ — interferon γ; COX-2 — cyclo-oxygenase-2; MMP — metalloproteinase; TIMP — tissue inhibitor of metalloproteinase

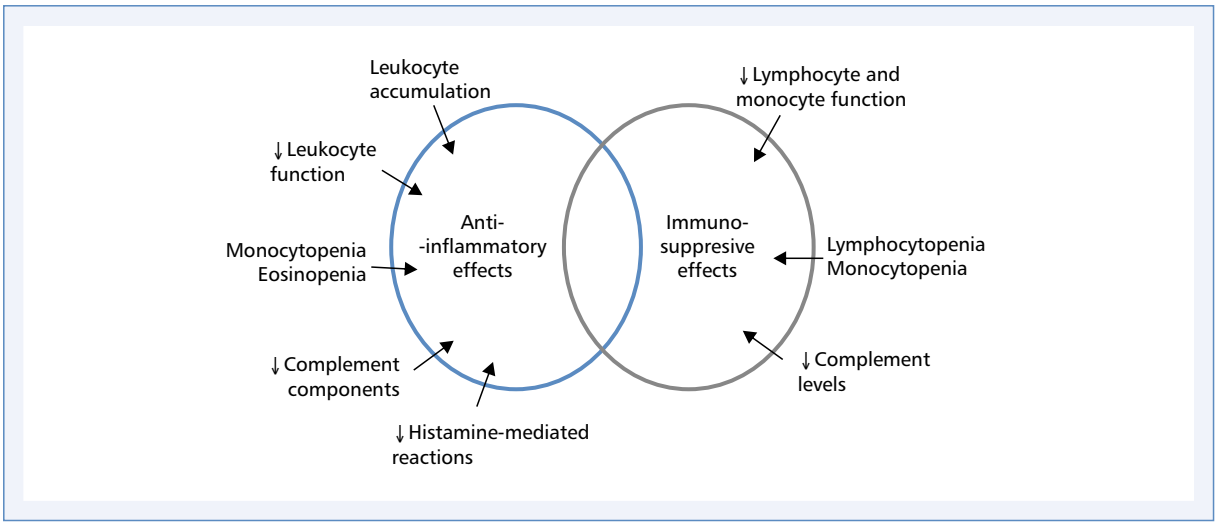

Figure 7C. Immunological basis for the lack of effects of immunotherapy in patients treated by immunosuppression — the physiological effect [29]

with diagnosis of such diseases as Crohn's disease, multiple sclerosis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, scleroderma, and ulcerative colitis.

At present, on the basis of available data, we conclude that an autoimmune disease is not an absolute contraindication for immunotherapy if strict clinical monitoring of the patients and a specialist consultation (e.g. rheumatologist, dermatologist) are ensured. We would, however, hesitate to offer this therapy in adjuvant treatment. In the case of patients with more severe autoimmune diseases (e.g. Guillain-Barré syndrome) one should be aware of the high risk of potential life-threatening complications and inform the patient. Patients with severe autoimmune diseases treated with biological drugs or who have life-threatening autoimmune disease complications (e.g. severe Crohn's disease) in their medical history should not be qualified for immunotherapy, in contrast to patients with minimal-symptom autoimmune disease (e.g. mild skin psoriasis). The qualification should be preceded by a conversation with the patient including discussing the consequences of an exacerbation of the autoimmune disease.

Summary

The blocking of immunological checkpoints dependent on CTLA-4 and PD-1 is an effective strategy of treating patients with a histologically confirmed diagnosis of skin or mucous membrane melanoma in stage III (non-resectable) or IV regardless of the status of the *BRAF* gene mutation. Immunotherapy can be considered already in the first-line treatment of all patients with melanoma (Figure 2) [3, 23]. The introduction of nivolumab, pembrolizumab, and ipilimumab into clinical practice has allowed an improvement in the prognosis for a large group of melanoma patients (Figure 3, 4). The use of these antibodies has yielded treatment results not observed earlier (Figure 5, 6). Nivolumab and pembrolizumab are better tolerated than ipilimumab because of their relatively low toxicity [5, 13]. Patients treated by immunotherapy when starting their treatment must have satisfactory parameters of morphology and blood biochemistry including the number of leucocytes $\geq 2000/\mu L$, the number of neutral granulocytes $\geq 1000/\mu L$, the number of platelets $\geq 75{,}000/\mu L$, haemoglobin concentration ≥ 9 g/dL or ≥ 5.6 mmol/L, serum creatinine concentration $\leq 1.5 \times$ GGN, AST/ALT activity $\leq 2.5 \times$ GGN, and total bilirubin concentration $\leq 1.5 \times$ GGN or direct bilirubin $\leq$ GGN in patients with total bilirubin levels > 1.5 GGN. At the same time, as is shown by analyses, immunotherapy with checkpoint inhibitors has similar effectiveness and toxicity in persons aged ≥ 65 years and < 65 years, and chronological age by itself should not exclude the use of these drugs [33]. Qualification for immunotherapy, however, has some limitations and contraindications due to its mechanism of action (Figure 1), and these are pre-existing active autoimmune diseases including Crohn's disease or multiple sclerosis, as well as the patient taking systemic immunosuppressive therapy based on corticosteroids and/or methotrexate (Figure 7) or immunosuppressive biological drugs [13]. Currently patients who have received live vaccines, with immune deficiency, active HIV infection, or another active infection including active tuberculosis are not qualified for immunotherapy. Infections with hepatitis B virus, hepatitis C virus, and HIV were almost universal exclusion criteria in investigations of immunological checkpoint inhibitors. It seems that these chronic infections could suppress T cell function and theoretically could decrease the effectiveness (particularly in the case of severe HIV/AIDS with a low number of CD4 + T cells) [34]. The principles of procedures for patients with a diagnosis of melanoma with metastases to the CNS have been described in the paper "Management of brain metastases in melanoma" (Piotr Rutkowski, Dorota Kiprian, Monika Dudzisz-Śledź, Tomasz Świtaj, Radosław Michalik, Mateusz Spałek, Katarzyna Kozak, Tomasz Mandat) [35], similarly to the principles of action in the case of combining immunotherapy with radiotherapy "The role of radiotherapy in melanoma" (Mateusz Spałek, Anna M. Czarnecka), which was also presented in "Oncology in Clinical Practice" [36].

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REVIEW ARTICLE

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Preoperative treatment of HER2-positive breast cancer

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ABSTRACT

Preoperative chemotherapy is more and more frequently used in the treatment of localized and locally-advanced breast cancer. This approach not only creates optimal conditions for organ-sparing surgery but also provides us with valuable information on the biology and chemosensitivity of cancer. This data is then crucial for the choice of systemic adjuvant therapy. The availability of two anti-HER2 targeted agents (pertuzumab and trastuzumab) for the neoadjuvant treatment of breast cancer significantly improves the efficacy of this approach. Significantly increased percentage of patients experiencing complete pathological response correlates with improved outcomes. This article is aimed at summarizing current knowledge regarding the role of pertuzumab in neoadjuvant treatment of HER2-positive breast cancer and comprises essential guidelines for the optimal use of currently reimbursed therapies in this disease.

Key words: neoadjuvant treatment, preoperative chemotherapy, HER2-positive, pertuzumab, trastuzumab, breast cancer

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Introduction

After a long waiting period, on September 1, 2019 the Ministry of Health issued a positive decision regarding reimbursement of pertuzumab in the preoperative treatment of patients with locally advanced HER2-positive breast cancer. The changes introduced into the drug program allow not only optimisation of safety but they also increase the effectiveness of neoadjuvant treatment. In contrast to the provisions of the drug program for palliative treatment of patients with HER2-positive breast cancer, which, based on the results of CLEOPATRA study [1] strictly defined treatment regimen based on the combination of pertuzumab and trastuzumab, in preoperative management various treatment regimens including these drugs can be used. Expanding treatment options with new regimens is always, especially in the first period, associated with many doubts about the optimal combination of drugs, taking into account their safety and effectiveness. This article summarises the current knowledge regarding the use of trastuzumab and pertuzumab in preoperative treatment, with particular emphasis on the possibility of using this drug in clinical practice in Poland.

The role of preoperative treatment

Preoperative treatment is one of the options for the management of patients with early breast cancer. Despite a number of studies comparing the benefits of neoadjuvant versus adjuvant therapy, the advantage of preoperative treatment in relation to patient prognosis has not been demonstrated. The main goal of neoadjuvant treatment is to increase the feasibility of surgical treatment in patients with initially inoperable, locally advanced tumour (IIIA–C and "inflammatory" breast cancer), in whom resection is impossible, or to create the possibility of breast-conserving surgery (BCS) in the case of primary operable tumours (T2 N0–1 M0). Preoperative chemotherapy allows an increase in the percentage of BSC procedures from a few to several per cent; however, in many patients, regardless of the response to systemic treatment, such a procedure cannot

be used due to the presence of objective contraindications. A recent meta-analysis comparing preoperative and postoperative treatment did not show differences according primary prognostic parameters. However, this analysis showed a significantly increased percentage of local recurrences in patients receiving preoperative treatment, which resulted from a much higher percentage of BCS procedures compared to patients who were undergoing primary surgical treatment [2].

Very important additional benefits associated with preoperative chemotherapy include early application of systemic treatment and obtaining information about the anti-tumour effect of the neoadjuvant treatment based on postoperative material examination. Confirmation of residual disease after preoperative treatment is an indication to consider adjuvant treatment with another cytotoxic drug (capecitabine in HER2-negative cancers or T-DM1 in HER2-positive cancers).

Pathological complete response

In modern clinical trials assessing different strategies of preoperative chemotherapy, the pathological complete response (pCR) rate is the most commonly used primary endpoint. Unfortunately, for years, this parameter was not standardised, and in many studies, different research groups defined it differently; in some studies only the breast tumour was assessed, in others lymph nodes were also included, and sometimes pCR could be found even if carcinoma in situ or single invasive cancer lesions were present [2]. The discrepancies in pCR definition between different studies make it very difficult to compare individual preoperative treatment strategies and perform meta-analyses that could clearly indicate the optimal neoadjuvant chemotherapy regimen.

However, there is no doubt that the effectiveness of preoperative treatment depends primarily on the histological type of breast cancer. The expression of steroid receptors and a low proliferative index correlate with a lower probability of obtaining pCR (6.4% *vs.* 31% for luminal subtype A and the so-called "triple negative" cancer, respectively) [3]. Based on, among other things, the combined analysis of the German Breast Group (GBG) studies, it is known that patients achieving a complete pathological response (ypT0 ypN0) after preoperative chemotherapy have a very good prognosis regarding disease-free survival (DFS, HR = 4.04; $P < 0.001$) and overall survival (OS, HR = 7.39; $P < 0.001$). In the case of HER2-positive breast cancer, the probability of pCR depends on the use of molecularly targeted therapies. In the mentioned GBG analysis the pCR rate after the use of pre-operative chemotherapy in patients with luminal B HER2-negative and HER2-positive breast cancer was about 11%, while the combination of chemotherapy and trastuzumab doubled this percentage (to 22%). For HER2-positive, oestrogen receptor-negative (OR-negative) and progesterone receptor-negative (PR-negative) cancer, the pCR rates were 28% and 33% for chemotherapy and combination chemotherapy with trastuzumab, respectively [3]. A meta-analysis involving more than 11,000 breast cancer patients undergoing neoadjuvant treatment showed a significantly increased pCR rate after chemotherapy with trastuzumab (31–50%) compared to chemotherapy alone (18–30%) in the HER2-positive breast cancer population [4]. Furthermore, this study showed a strong relationship between pCR and prognosis in patients with HER2-positive/ER-negative/PR-negative breast cancer receiving trastuzumab in neoadjuvant therapy (EFS, HR = 0.15, 95% CI 0.09–0.27; OS, HR = 0.08, 95% CI 0.03–0.22).

Preoperative treatment of HER2-positive breast cancer

HER2 receptor overexpressed in breast cancer cells is one of the key mechanisms responsible for the high aggressiveness of the cancer, while being a critical therapeutic target. In 1998, trastuzumab (a monoclonal antibody that binds and inactivates HER2 receptor) was registered in the treatment of patients with metastatic breast cancer, and in 2006 the registered indications were expanded to include adjuvant treatment based on studies that showed a significant improvement of prognosis [5–7].

More than nine years ago, the first evidence regarding the efficacy and safety of preoperative chemotherapy combined with trastuzumab in patients with HER2-positive breast cancer was reported. Since then, several subsequent clinical trials have been conducted assessing various neoadjuvant chemotherapy regimens with trastuzumab. In the following years, with the advent of new anti-HER2 drugs active in generalised HER2-positive breast cancer (pertuzumab and lapatinib), assessment of the possibility of combining these drugs within neoadjuvant treatment was also started. The purpose of the combination of anti-HER2 drugs was to increase the likelihood of a response and improve safety (primarily to reduce the risk of cardiotoxicity) by reducing the intensity of chemotherapy included in preoperative treatment [8–11]. Table 1 summarises the studies assessing preoperative regimens containing anti-HER2 antibodies.

Combination of anti-HER2 drugs with anthracyclines

In some studies assessing the role of trastuzumab in preoperative treatment, it was used concomitantly

Table 1. Summary of clinical studies evaluating trastuzumab in neoadjuvant treatment. P — paclitaxel, T — trastuzumab, A — doxorubicin, C — cyclophosphamide, D — docetaxel (D75 — 75 mg/m^2 q3w, D100 — 100 mg/m^2 q3w, D75/100 — dose escalation possible), E — epirubicin, F — 5-fluorouracil, K — carboplatin, M — methotrexate, PER — pertuzumab

Study	Number of patients	Regimen	pCR	Ref.
MDACC	23	4 × P + T → 4 × FEC + T	65%	[12]
NOAH	117	3 × AP + T → 3 × P + T → 3 × CMF + T	38%	[11]
NeoALLTO	149	T → T + 12 × P	28%	[13]
HannaH	299	4 × D75 + T → 4 × FEC + T	34%	[14]
GeparQuinto	309	4 × EC + T → 4 × D100 + T	30%	[15]
ACOSOG Z1041	140	4 × FEC → 12 × P + T	48%	[16]
	142	12 × P + T → 4 × FEC + T	47%	
NSABP B-41	181	4 × AC → 4 × P + T	49%	[7]
REMAGUS 2	62	4 × EC → 4 × D100 + T	26%	[17]
GEICAM/2006-14	50	4 × EC → 4 × D100 + T	48%	[18]
CHER-LOB	36	12 × P + T → 4 × FEC + T	25%	[19]
PCH	29	12 × P + K + T	69%	[20]
NeoSphere	107	4 × D(75/100) + T	29%	[10]
	107	4 × D(75/100) + PER + T	46%	
	107	4 × PER + T	17%	
	96	4 × D(75/100) + PER	24%	
TRYPHAENA	72	3 × FEC + PER + T → 3 × DXL(75/100) + PER + T	61%	[11]
	75	3 × FEC → 3 × DXL(75/100) + PER + T	57%	
	76	6 × D75 + K + T + PER (TCHP)	66%	
KRISTINE	221	6 × D75 + K + T + PER (TCHP)	56%	[21]
	223	T-DM1 + PER	44%	

with anthracyclines, although this combination is associated with a high risk of myocardial insufficiency and is generally not recommended for adjuvant and palliative treatment. Despite this, in several studies (e.g. NOAH, GeparQuinto, ACOSOG Z1041, HannaH, or Cher-Lob) in which trastuzumab was associated with anthracycline-containing regimens (a total of over 1000 patients), no clinically significant increase of cardiotoxicity risk was observed [14, 16, 19, 22]. There is no doubt, however, that patients participating in these trials were subject to very close cardiological monitoring, which is not a standard in routine clinical practice. Therefore, the use of preoperative chemotherapy regimens combining trastuzumab with anthracyclines is not recommended.

One of the reasons for combining anthracyclines with trastuzumab as part of preoperative treatment was an attempt to increase the effectiveness of classic neoadjuvant chemotherapy regimens, usually based on anthracyclines and taxoids. According to assumptions, concomitant use of trastuzumab with all cycles of preoperative chemotherapy should have been more effective than using this drug only during taxoid administration. However, the majority of studies on preoperative treatment of HER2-positive breast cancer patients did not allow conclusions to be drawn about the real benefits of concurrent use of trastuzumab and anthracyclines, because they did not compare two trastuzumab administration regimens in parallel. In the phase III ACOSOG Z1041 study, 282 patients with initially operable HER2-positive breast cancer were randomly assigned (1:1) to a sequential arm receiving the 4 × FEC → 12 × PXL 80 mg/m^2 + trastuzumab or to a concurrent arm with the regimen 12 × PXL + trastuzumab → 4 × FEC. No significant difference was seen in pCR rate (primary endpoint) between study arms; pCR was reported in 56.5% of patients in the sequential arm and 54.2% in the concurrent arm (OR = 0.90; 95% CI 0.55–1.49). The deterioration of left ventricular function (G1–4 and G3–4 according to WHO CTC) was observed in 3.6% and 0% of patients in the sequential arm and 8.4% and 0.7% in the concurrent arm, respectively [14]. The three-arm, phase II TRYPHAENA study compared in two arms concurrent or sequential use of FEC regimen with the combination of pertu-

zumab and trastuzumab (FEC + trastuzumab + pertuzumab → docetaxel + trastuzumab + pertuzumab *vs.* FEC → docetaxel + trastuzumab + pertuzumab) [11]. In this study, pCR rates were 51% in the concurrent arm and 45% in the sequential arm, but the risk of neutropaenic fever was clearly higher in the concurrent arm than in the sequential arm (18% *vs.* 9%) with comparable cardiotoxicity.

Optimal combination of pertuzumab with trastuzumab and chemotherapy in preoperative treatment

Compared to the number of clinical studies on the role of trastuzumab in the preoperative treatment of patients with HER2-positive breast cancer, the number of studies on the combination of trastuzumab with pertuzumab is significantly smaller. Many early studies on trastuzumab focused on the potential for reducing the intensity of chemotherapy by excluding anthracyclines. A study conducted by Hurley et al. involved 48 patients with locally advanced or inflammatory HER2-positive breast cancer. Preoperative treatment administered for 12 weeks (docetaxel 70 mg/m^2 d. 1 + cisplatin 70 mg/m^2 d. 1 + weekly trastuzumab — four courses in total) led to a pathological complete response in 23% of patients [23]. Another study looked at the activity of combination of carboplatin at a dose of AUC6 + paclitaxel 80 mg/m^2 and trastuzumab at a weekly dose during 12 weeks of preoperative treatment in patients with operable (majority of patients) HER2-positive breast cancer. Pathological complete responses were observed in a surprisingly high percentage of patients (76%), which could be a consequence of enrolment of patients with small tumours [20]. In another phase II study of neoadjuvant chemotherapy without anthracycline, 56 patients with HER2-positive breast cancer (IIB–IIIC) were randomly assigned to two preoperative chemotherapy regimens based on the combination of trastuzumab, carboplatin, and paclitaxel (PXL 175 mg/m^2 + carboplatin AUC6 + trastuzumab in a three-week schedule — a total of four courses or PXL 80 mg/m^2 d. 1, 8, 15 + carboplatin AUC2 d. 1, 8, 15 + trastuzumab on a weekly basis — four courses in total). In the weekly chemotherapy arm a significant increase of pCR rate, from 40.7% to 69% (HR = 0.3; 95% CI 0.1–0.9), was observed, which was particularly marked in patients with hormone-dependent and HER2-positive breast cancer — 67% *vs.* 21% (71% *vs.* 62% in ER-negative/PR-negative tumours) [24]. The percentage of side effects was similar in both arms.

A key study on the role of pertuzumab in preoperative treatment (phase II NeoSphere study) [10] even allowed for complete abandonment of chemotherapy before surgery. In this study, 417 HER2-positive breast cancer patients were randomly assigned to preoperative treatment according to the schedules — (i) 4 × docetaxel + trastuzumab, (ii) 4 × docetaxel + trastuzumab + pertuzumab, (iii) 4 × trastuzumab + pertuzumab, and (iv) 4 × docetaxel + pertuzumab. After surgery, all patients received anthracycline-based adjuvant therapy with trastuzumab for up to 12 months, and patients in the non-chemotherapy arm also received docetaxel. The NeoSphere study showed the highest pCR rate in the arm receiving a three-drug regimen (docetaxel + trastuzumab + pertuzumab) — 46%, compared to 29% (docetaxel + trastuzumab), 24% (docetaxel + pertuzumab), and 17% (pertuzumab + trastuzumab). This study also showed no additional toxicity associated with the addition of pertuzumab.

In the aforementioned TRYPHAENA study, in addition to anthracycline-containing regimens, the efficacy and safety of a docetaxel, carboplatin, and trastuzumab with pertuzumab regimen (TCHP) were also assessed. In this arm, a very high pCR rate of 64% was achieved at the expense of side effects such as febrile neutropaenia (17% of patients), G3 diarrhoea (12%), G3 anaemia (17%), and thrombocytopaenia (12%).

In the phase III KRISTINE study comparing the experimental regimen with trastuzumab emtansine (T-DM1) and pertuzumab *versus* TCHP in preoperative treatment, a high pCR rate of 55.7% was confirmed in the TCHP arm (221 patients) *versus* 44.4% in the experimental arm [21].

Regimens of preoperative chemotherapy in HER2-positive breast cancer

Trastuzumab *s.c.* — 600 mg *s.c.*; dosing every three weeks
Trastuzumab *i.v.* — 8 mg/kg (first loading dose) then 6 mg/kg *i.v.*; dosing every three weeks
Pertuzumab — 840 mg *i.v.* (loading dose followed by 420 mg *i.v.*) — every 3 week

AC → PTP
Four cycles — doxorubicin 60 mg/m^2 *i.v.* + cyclophosphamide 600 mg/m^2 *i.v.* d. 1 every three weeks, then paclitaxel 80 mg/m^2 *i.v.* d. 1 weekly for 12 weeks + trastuzumab* + pertuzumab**
After surgery trastuzumab should be continued for up to a year.

AC → DTP
Four cycles — doxorubicin 60 mg/m^2 *i.v.* + cyclophosphamide 600 mg/m^2 *i.v.* d. 1 every three weeks, then four cycles — docetaxel 100 mg/m^{2*} *i.v.* d. 1 every three weeks + trastuzumab* + pertuzumab**

After surgery trastuzumab should be continued for up to a year.

EC → DTP
Four cycles — epirubicin 90 mg/m^2 *i.v.* + cyclophosphamide 600 mg/m^2 *i.v.* d. 1 every three weeks, then
four cycles — docetaxel 100 mg/m^{2*} *i.v.* d. 1 every three weeks + trastuzumab*+ pertuzumab**
After surgery trastuzumab should be continued for up to a year.

EC → PTP
Epirubicin 75 mg/m^2 *i.v.* + cyclophosphamide 500 mg/m^2 *i.v.* d. 1 every three weeks, then
paclitaxel 80 mg/m^2 *i.v.* weekly for 12 weeks + trastuzumab* + pertuzumab**
After surgery trastuzumab should be continued for up to a year.

TCHP
Six cycles — docetaxel 75 mg/m^2 *i.v.* + carboplatin AUC6 *i.v.* + trastuzumab* + pertuzumab**
After surgery trastuzumab should be continued for up to a year.

PCHP
Four cycles — paclitaxel 80 mg/m^2 *i.v.* d. 1, 8, 15 + carboplatin AUC2 *i.v.* d. 1, 8, 15, concomitantly trastuzumab* + pertuzumab**
After surgery trastuzumab should be continued for up to a year.

Summary

The introduction of anti-HER2 drugs significantly improved the effectiveness of neoadjuvant treatment in HER2-positive breast cancer patients. Without a significant increase in toxicity, it was possible to achieve a significant increase in pCR rate and increase the percentage of patients undergoing breast-conserving surgery. The current changes in the "Breast Cancer Treatment" drug program finally allow us to offer patients with HER2-positive breast cancer effective and safe preoperative treatment in line with international standards in the case of local advancement (N+) or planned breast-conserving surgery in patients with a tumour of diameter > 2 cm. When applying preoperative treatment in patients with HER2-positive breast cancer, it should be remembered that the use of trastuzumab is not the only condition for obtaining the expected clinical benefits. The maximum effectiveness of neoadjuvant treatment is guaranteed by the use of an optimal combination of chemotherapy with anti-HER2 drugs and the maintenance of the originally planned dose intensity. It should also be remembered that the combination of trastuzumab and pertuzumab with docetaxel monotherapy (as in the NeoSphere study) is not a recommended preoperative treatment because of the need for use of anthracycline-containing adjuvant chemotherapy. The use of only the docetaxel + trastuzumab + pertuzumab combination not only reduces the likelihood of obtaining pCR, but also precludes or significantly delays postoperative use of trastuzumab. If there is any doubt about the tolerability of the planned treatment, alternative chemotherapy regimens (e.g. with lower cardiotoxic potential — anthracycline-free regimens) or showing a lower risk of myelosuppression (weekly regimens) should be considered. As in the case of adjuvant treatment, unjustified dose reductions of cytotoxic drugs (e.g. in obese patients [12]) are unfavourable in terms of the probability of response and patient prognosis, and they should be considered primarily if unacceptable tolerance of treatment occurs.

*Trastuzumab — [intravenous formulation] 8 mg/kg *i.v.* (loading dose) followed by 6 mg/kg *i.v.* — every 3 weeks; [subcutaneous formulation] — 600 mg *s.c.* — every 3 weeks

**Pertuzumab — 840 mg/kg *i.v.* (loading dose) followed by 420 mg/kg *i.v.* — every 3 weeks

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VIA MEDICA

REVIEW ARTICLE

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Encorafenib in combination with binimetinib — a new therapeutic option with a favourable safety profile in the treatment of patients with advanced *BRAF* mutation-positive melanoma

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ABSTRACT

Encorafenib and binimetinib were registered in 2018 for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF V600* mutation. The results of the phase III study (Columbus) are very promising. Median PFS for patients who have received this treatment was 14.9 months, and the median OS was 33.6 months. The reduction of toxicity is the reason for the unique pharmacokinetic profile of this therapy. Knowledge about the adverse evets is important in the context of optimizing and individualizing treatment.

Key words: encorafenib, binimetinib, *BRAF*, melanoma, adverse events, safety of treatment

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In about 50% patients with a melanoma diagnosis in the dissemination stage, a *BRAF* gene mutation most commonly in exon 15 (over 95% cases) is detected. It causes the activation of mitogen-activated protein kinase (MAPK), which leads to the development and progression of melanoma [1]. The introduction of BRAF inhibitors (BRAFi) — vemurafenib in 2011 and dabrafenib in 2012 — caused a significant improvement in progression-free survival (PFS) and overall survival (OS) in comparison with the used then dacarbazine-based chemotherapy [2].

The advantages of using BRAFi in monotherapy are, however, limited mainly because of the emerging resistance due to MAPK pathway reactivation. Double inhibition of the MAPK pathway by using combined therapy based on BRAFi and MEKi (MEK inhibitors) allowed an improvement in results of treatment with decreased toxicity [3]. Among standard methods of treating patients with advanced melanoma are three combinations of BRAFi/MEKi (vemurafenib/cobimetinib, dabrafenib/trametinib, and encorafenib/binimetinib) [4]. The two first combinations have a comparable effectiveness in the context of treatment, with a median PFS of about 12 months and median OS of about 24 months. The above-mentioned drugs differ in their safety profiles and the occurring adverse events. For instance, fever was observed in 51–53% of patients treated with dabrafenib/trametinib, and this was the main reason for treatment interruption (in 30–32%) or dose reduction (13–14%). In turn, the strongest photosensitising effects were observed in the group of patients treated with vemurafenib/cobimetinib (in 48%) [2, 5].

On the basis of the results of a phase III trial (COLUMBUS), a third combination of drugs — encorafenib and binimetinib — was registered in the United States and in the European Union in 2018 for treating patients with advanced melanoma and *BRAF* mutation. Median PFS for patients receiving this treatment was 14.9 months, and median OS was 33.6 months [5]. Adverse events of any grade were reported less frequently in this group in comparison with patients treated with dabrafenib/trametinib or vemurafenib/cobimetinib [2, 5].

Encorafenib was found to have a long half-life (> 30 hours) in comparison with dabrafenib (2 hours) or vemurafenib (0.5 hours). Moreover, IC50 (one half of the maximal inhibitory concentration) is 40 nmol/l or less in most melanoma cell lines. For comparison, a higher concentration of dabrafenib (< 100 nmol/l) and a much higher concentration of vemurafenib (< 1 μmol/l) is required to inhibit proliferation in most cell lines, which may translate into a higher efficacy of encorafenib treatment with a simultaneous reduction in toxicity [4, 6].

One of the more serious adverse events after monotherapy with BRAF inhibitors is the induction of secondary neoplasms — most frequently cutaneous squamous-cell carcinoma (cuSCC). This is linked to paradoxical ERK activation or hyperactivation of ERK signalling by BRAF inhibitors in cells without the *BRAF* mutation (*BRAF* wild-type cells). The index of cuSCC induction is highly differentiated depending on the used BRAF inhibitor because ERK activation and the time of activation are unique for each inhibitor [6].

In 2016, in the biweekly Oncotarget, the results of studies performed at the MD Anderson University in Texas by Adelmann et al. were published, comparing the ranges of BRAF inhibitor concentrations (vemurafenib, dabrafenib, encorafenib LGX818 and PLX8394) required for paradoxical ERK activation. Encorafenib had the highest paradox index. This means that in comparison with other inhibitors it causes cuSC0,C to a much smaller extent, and a higher drug concentration is much better tolerated. Adverse events linked to paradoxical ERK activation are more common in the case of therapy with vemurafenib (18–19%) and dabrafenib (6–10%) in comparison with encorafenib (4%) [7].

So far, no clinical trial has been conducted directly comparing the action and safety profile of vemurafenib/cobimetinib, dabrafenib/trametinib, and encorafenib/binimetinib, and indirect comparison of the used combinations between clinical trials is of limited value.

Analysis of the results of phase III trials in which basic safety parameters were compared for dabrafenib/trametinib (COMBI-v), vemurafenib/cobimetinib (coBRIM), and encorafenib/binimetinib (COLUMBUS) is presented in Table 1. What is important, each trial comprised a comparative arm with 960 mg vemurafenib given two times per day [8]. Patients included in individual trials had similar characteristics; however, the proportion of persons with initial higher LDH activity above the upper range of the normal value in the coBRIM trial was higher than in the COMBI-v and COLUMBUS trials [8, 9].

The results of the first part of the phase III COLUMBUS trial indicate that encorafenib and binimetinib together show a favourable profile of effectiveness and tolerance, which is indicated by attainment of a higher median of dose intensity with a longer exposure to treatment. For the Columbus trial altogether 577 patients were randomised, and 570 who received treatment were included in the analysis of the safety profile. Patients were randomised in a 1:1:1 ratio (192 — encorafenib and binimetinib, 192 — encorafenib in monotherapy, 186 — vemurafenib in monotherapy). The median exposure time to the analysed treatment was greatest in the branch in which encorafenib was used in combination with binimetinib, and it was 51 weeks in comparison to using encorafenib in monotherapy (31 days) and vemurafenib in monotherapy (27 weeks) [10].

Knowledge of the safety profile, characteristic adverse events for selected combinations, and the potential time of their occurrence after initiation of therapy (Table 2) is important in the context of selection and optimisation of treatment in particular groups of patients [5]. The most important undesirable effects reported in the Columbus registration trial were evaluated by CTCAE (Common Terminology Criteria for Adverse Events) criteria and are presented in Figure 1.

Fever

In the COLUMBUS trial fever was reported much more frequently during vemurafenib treatment (in 30%). Encorafenib in monotherapy and in combination with binimetinib can also cause fever (in the COLUMBUS trial it was observed, respectively, in 16% and 18% patients), but it was reported much later after the moment of treatment initiation (median time to first occurrence 85 days [1–560] (Table 2) in comparison with vemurafenib — 19 days [2–619]). In general, in patients treated with encorafenib and binimetinib, this undesirable effect was grade 1, but was rarely the cause of dose reduction (4%) and interruption of treatment l (1 patient: < 1%) [5]. Fever for the encorafenib and binimetinib combination was in general limited to a single episode and was rarely recurrent (only in 5% patients), in contrast to the dabrafenib and trametinib combination, where it occurred much more frequently and was more often recurrent [8]. In the COMBI-V trial in the group of patients treated with dabrafenib and trametinib, fever was the most common reason for interrupting treatment

Table 1. Frequency of adverse events in combined therapy, which occurred in key clinical trials comparing BRAFi/MEKi combinations with vemurafenib [8]

Combination	Dabrafenib + trametinib		Vemurafenib + cobimetinib		**Encorafenib + binimetinib**	
Date at moment of analysis	13.03.2015		30.09.2015		19.05.2016	
Name of clinical trial	COMBI-V		coBRIM		COLUMBUS part 1	
All patients of treated population (analysis in agreement with planned treatment)	352 (350)		247 (247)		192 (192)	
Daily drug dose [mg]	300 + 2		1920 + 60		450 + 90	
Toxicity grade according to CTC AE	All	3–4	All	3–4	All	3–4
Skin complications [n (%)]						
Rash	84 (24.0)	3 (0.9)	101 (40.9)	13 (5.3)	27 (14.1)	2 (1.0)
Maculopapular rash	13 (3.7)	2 (0.6)	38 (15.4)	18 (7.3)	3 (1.6)	0
Dry skin	33 (9.4)	0	38 (15.4)	2 (0.8)	27 (14.1)	0
Pruritus	36 (10.3)	0	49 (19.8)	3 (1.2)	21 (10.9)	1 (0.5)
Erythema	35 (10.0)	0	26 (10.5)	0	13 (6.8)	0
Acne dermatitis	23 (3.6)	0	34 (13.8)	6 (2.4)	6 (3.1)	0
Baldness	23 (6.6)	0	41 (16.6)	1 (0.4)	26 (13.5)	0
Hyperkeratosis	18 (5.1)	0	25 (10.1)	1 (0.4)	27 (14.1)	1 (0.5)
Keratosis of hands and feet	–	–	5 (2.0)	0	17 (8.9)	0
Palmoplantar erythrodysesthesia	14 (4.0)	0	17 (6.9)	0	13 (6.8)	0
Solar keratosis	5 (1.4)	0	13 (5.3)	8 (3.2)	–	–
Keratosis pilaris	4 (1.1)	0	9 (3.6)	0	9 (4.7)	0
Hypersensitivity to light	15 (4.3)	0	84 (34.0)	1 (0.4)	8 (4.2)	1 (0.5)
Sunburn	3 (0.9)	0	37 (15.0)	2 (0.8)	0	0
Cutaneous squamous cell carcinoma	5 (1.4)	5 (1.4)	10 (4.0)	9 (3.6)	5 (2.6)	0
Keratoacanthoma	2 (0.6)	2 (0.6)	4 (1.6)	3 (1.2)	4 (2.1)	0
Skin papilloma	8 (2.3)	0	17 (6.9)	0	12 (6.3)	0
Basal cell carcinoma	3 (0.9)	2 (0.6)	15 (6.1)	14 (5.7)	3 (1.6)	0
Gastrointestinal complications [n (%)]						
Diarrhoea	120 (34.3)	4 (1.1)	150 (60.7)	16 (6.5)	70 (36.4)	5 (2.6)
Nausea	126 (36.0)	1 (0.3)	105 (42.5)	3 (1.2)	79 (41.1)	3 (1.6)
Vomiting	107 (30.6)	4 (1.1)	63 (25.5)	4 (1.6)	57 (29.7)	3 (1.6)
Stomachache	39 (11.1)	1 (0.3)	27 (10.9)	1 (0.4)	32 (16.7)	5 (2.6)
Upper stomach pain	33 (9.4)	–	12 (4.9)	0	23 (12.0)	2 (1.0)
Constipation	54 (15.4)	0	27 (10.9)	0	42 (21.9)	0
General symptoms [n (%)]						
Tiredness	110 (31.4)	4 (1.1)	91 (36.8)	11 (4.5)	55 (28.6)	4 (2.1
Weakness	61 (17.4)	5 (1.4)	47 (19.0)	5 (2.0)	35 (18.2)	3 (1.6)
Fever	193 (55.1)	16 (4.6)	71 (28.7)	3 (1.2)	35 (18.2)	7 (3.6)
Oedema/peripheral oedema	48 (13.7)	1 (0.3)	34 (13.8)	0	3 (1.6)	0
Headache	112 (32.0)	4 (1.1)	44 (13.8)	1 (0.4)	42 (21.8)	3 (1.6)
Vertigo	34 (9.7)	1 (0.3)	15 (6.1)	0	24 (12.5)	3 (1.6)
Abnormalities in laboratory results during BRAFi/MEKi treatment [n (%)]						
Increased ALT concentration	49 (14.0)	9 (2.6)	65 (26.3)	28 (11.3)	21 (10.9)	10 (5.2)
Increased AST concentration	42 (12.0)	5 (1.4)	60 (24.3)	22 (8.9)	16 (8.3)	4 (2.1)
Increased GGTP concentration	38 (10.9)	19 (5.4)	54 (21.9)	36 (14.6)	29 (15.1)	18 (9.4)

→

Table 1. cont. Frequency of adverse events in combined therapy, which occurred in key clinical trials comparing BRAFi/MEKi combinations with vemurafenib [8]

Combination	Dabrafenib + trametinib		Vemurafenib + cobimetinib		Encorafenib + binimetinib	
Increased ALP concentration	26 (7.4)	7 (2.0)	42 (17.0)	12 (4.9)	16 (8.3)	1 (0.5)
Increased CPK concentration	10 (2.9)	6 (1.7)	87 (35.2)	30 (12.1)	44 (22.9)	13 (6.8)
Increased creatinine concentration	15 (4.3)	0	37 (15.0)	3 (1.2)	12 (6.3)	2 (1.0)
Increased lipase concentration	–	–	9 (3.6)	8 (3.2)	4 (2.1)	3 (1.6)
Hyperglycaemia	17 (4.9)	8 (3.2)	8 (3.2)	1 (0.4)	9 (4.7)	4 (2.1)
Hyponatraemia	16 (4.6)	15 (4.3)	13 (5.3)	7 (2.8)	2 (1.0)	1 (0.5)
Anaemia	26 (7.4)	7 (2.0)	39 (15.8)	4 (1.6)	29 (15.1)	8 (4.2)
Neutropenia	32 (9.1)	17 (4.9)	3 (1.2)	0	5 (2.6)	2 (1.0)
Undesirable effects linked to the musculoskeletal system [n (%)]						
Joint pain	93 (26.6)	3 (0.9)	94 (38.1)	6 (2.4)	49 (25.5)	1 (0.5)
Pain in extremities	45 (12.9)	4 (1.1)	29 (11.7)	3 (1.2)	21 (10.9)	2 (1.0)
Muscle pain	66 (18.8)	0	37 (15.0)	4 (0.4)	26 (13.5)	0
Cardiovascular events [n (%)]						
QT prolongation (EKG)	5 (1.4)	2 (0.6)	11 (4.5)	3 (1.2)	0	0
cardiac ejection fraction decrease	29 (8.3)	13 (3.7)	29 (11.7)	5 (2.0)	11 (5.7)	2 (1.0)
Hypertension	103 (29.4)	54 (15.4)	39 (15.8)	15 (6.1)	21 (10.9)	11 (5.7)
Eye complications [n (%)]						
Blurred vision	17 (4.9)	0	28 (11.3)	0	30 (15.6)	0
Central serous chorioretinopathy	2 (0.6)	0	32 (13.0)	2 (0.8)	5 (2.6)	2 (1.0)
Retinal detachment	–	–	22 (8.9)	5 (2.0)	15 (7.8)	1 (0.5)
Lung complications [n (%)]						
Cough	77 (22.0)	0	23 (9.3)	0	16 (8.3)	1 (0.5)
Pneumonia	2 (0.6)	0	6 (2.4)	3 (1.2)	3 (1.2)	3 (1.6)
Embolism	7 (2.0)	7 (2.0)	2 (0.8)	2 (0.8)	6 (3.1)	2 (1.0)
Kidney-derived complications [n (%)]						
Acute kidney injury	4 (1.1)	4 (1.1)	7 (2.8)	3 (1.2)	3 (1.6)	2 (1.0)
Dehydration	15 (4.3)	6 (1.7)	11 (4.5)	5 (2.0)	11 (4.5)	5 (2.0)

for a certain time (30–32%), dose reduction (13–14%), or stopping the drugs (2–3%) [8, 11].

Undesirable gastrointestinal tract reactions (nausea, vomiting, and diarrhoea)

The frequency of nausea was similar during treatment with encorafenib and binimetinib (41%), encorafenib in monotherapy (39%), and vemurafenib in monotherapy (34%). In the group treated using the drug combination grade 1 nausea was observed in 24% patients, grade 2 in 15%, and grade 3 in 2% [5].

Vomiting was more characteristic for the group treated with encorafenib in combination and in monotherapy (respectively, 30% and 27%), and in the group receiving vemurafenib vomiting was reported in 16% of cases. In the group receiving encorafenib together with binimetinib, 18% had grade 1 vomiting, 10% grade 2, and 2% grade 3 [5].

Diarrhoea was dominant in persons treated with encorafenib in combination with binimetinib (36%) and vemurafenib in monotherapy (34%) but only in 14% of patients receiving encorafenib in monotherapy. In patients treated using the combination in general, grade 1 diarrhoea was reported in 24%, and less frequently grade 2 (10%), 3 (2%), and 4 (0.5%) [5].

The above undesirable gastrointestinal tract effects required a dose modification. In the branch with the combination in 8% patients with nausea, 7% with vomiting, and 4% with diarrhoea, and in 1% diarrhoea was the reason for stopping treatment. The median time from start of treatment to the first occurrence of symptoms was, in the case of nausea, 29 days (1–614 days), vomiting — 57 days (1–607 days), and diarrhoea — 29 days (1–534 days) [5].

Table 2. Adverse events of encorafenib and binimetinib in the COLUMBUS trial [5]

Adverse event (regardless of the grade of toxicity)	Median time to occurrence of adverse events in days (time interval)	Stopping treatment because of adverse events (%)	Dose reduction (%)
Nausea	29 (1–614)	0	8
Diarrhoea	29 (1–534)	1	4
Central serous retinopathy	38 (1–532)	0	6
Vomiting	57 (1–607)	0	7
Hyperkeratosis	77 (1–408)	0	2
Hypersensitivity to light	84 (1–677)	0	1
Fever	85 (2–545)	< 1	4
Joint pain	85 (1–708)	0	2
Left ventricle dysfunction	109 (1–648)	0	6

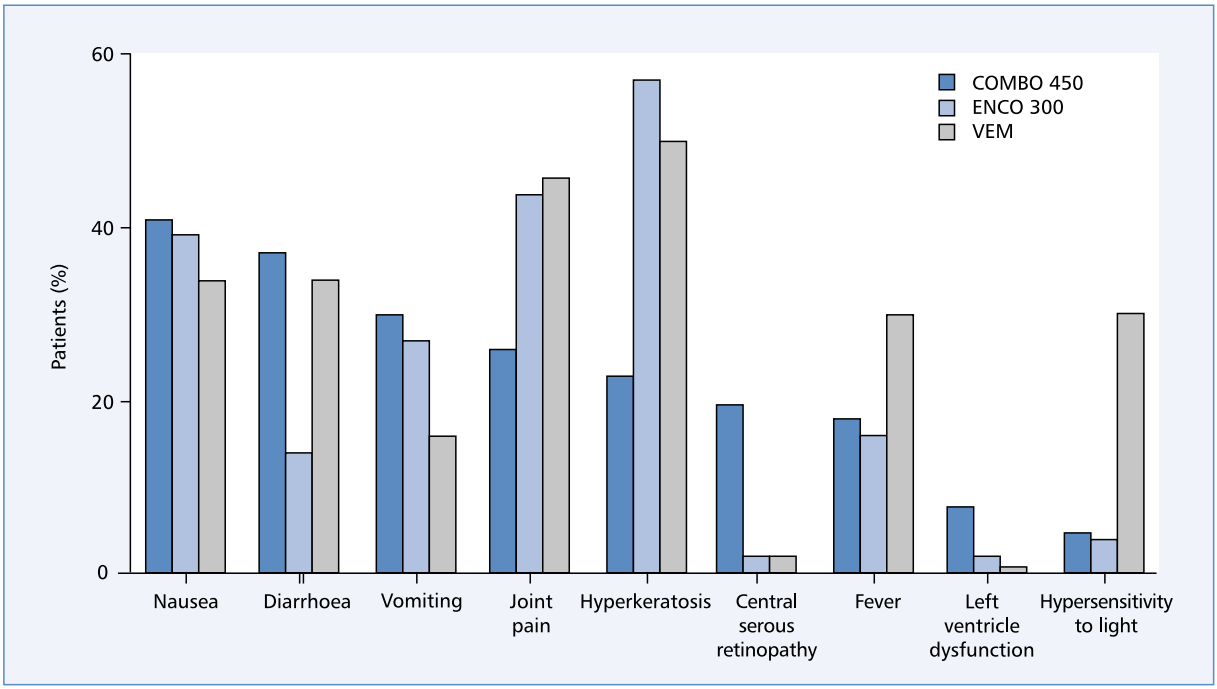

Figure 1. Selected adverse events occurring in patients (of all grades according to CTCAE) in any analysed group; COMBO 450 (450 mg encorafenib once a day plus 45 mg binimetinib twice a day); ENCO 300 (300 mg encorafenib once a day); VEM (960 mg vemurafenib twice a day) [5]

Joint pain

The frequency of occurrence of joint pain was lower in the case of encorafenib with binimetinib (26%), encorafenib in monotherapy (44%), and vemurafenib in monotherapy (46%). The median time from the moment of initiating combined therapy to the first appearance of symptoms was 85 days (1–708 days), and serious joint complications were rare (1% at grade 3). None of the patients required cessation of the therapy or reduction of the dose of drugs for this reason [5].

Hyperkeratosis

The frequency of hyperkeratosis occurrence was lower in the case of encorafenib and binimetinib (23%) than for encorafenib in monotherapy (57%) or vemurafenib in monotherapy (49%). The median time from the moment of initiating combined therapy to the first appearance of symptoms was 77 days (1–408 days). In 2% patients a reduction in drug dose was required, but in no case was treatment interrupted for this reason [5].

Hypersensitivity to light

The frequency of occurrence of hypersensitivity to light in the COLUMBUS trial was lower in the case of encorafenib and binimetinib (5%) and encorafenib (4%) in comparison with vemurafenib (30%). Median time from the moment of initiating combined therapy to the first appearance of symptoms was 84 days (1–677 days). Treatment was not interrupted for this reason in any of the patients, but one patient in the combined therapy group required a dose reduction [5, 8]. For comparison, hypersensitivity to light for vemurafenib and cobimetinib was often recurrent and long-term, which is indubitably related to the pharmacokinetic profile of the drugs [12].

Central serous retinopathy

Central serous retinopathy in the COLUMBUS trial was more frequent in patients treated with encorafenib and binimetinib (20%) in comparison with patients receiving encorafenib (2%) or vemurafenib (2%) in monotherapy. The median time from the moment of initiating combined therapy to the first appearance of symptoms was 38 days (1–532 days). In patients receiving the combination of drugs, grade 1 adverse effects (asymptomatic form) occurred in 12%, grade 2 in 5%, and grade 3 in 3%. In 6% of patients treated with encorafenib and binimetinib, the treatment required a periodic interruption and then a dose reduction, but in no patients was treatment stopped for this reason [5]. In general, central serous retinopathy was a reversible adverse effect. Most patients in whom it developed did not require a pharmacological intervention; however, topically used nonsteroidal anti-inflammatory drugs or carbonic anhydrase inhibitors can be useful in symptomatic treatment [8].

Left ventricle dysfunction (LVD) and other cardiovascular dysfunctions

Left ventricle dysfunction in the COLUMBUS trial was more commonly reported for encorafenib and binimetinib (8%) than for encorafenib in monotherapy (2%) or vemurafenib in monotherapy (1%). Median time from the moment of initiating combined therapy to the first appearance of symptoms was 109 days (1–648 days). Six per cent of patients receiving combined therapy required a periodic interruption of therapy with a subsequent dose reduction, but in no patients was treatment stopped for this reason. Left ventricle dysfunction was in general reversible [5].

In general, QT elongation during treatment is due to BRAFi — the phenomenon was observed in 3–7% patients treated with vemurafenib in monotherapy and in 2% treated with vemurafenib in combination with cobimetinib. QT elongation on this scale was not observed during therapy with dabrafenib or encorafenib, which is related to the chemical structure; these drugs contain an additional fluoridated phenyl ring. It is worth noting that the effect on QT elongation may be due to water-electrolyte perturbations (e.g. in the course of diarrhoea or using other drugs, e.g. proton pump inhibitors and fluoroquinolones). It is important that the EKG be evaluated before initiating treatment, and then every month for the first three months of inhibitor therapy, and then every 12 weeks. Treatment should be stopped when QTc attains a value of > 500 ms or increases by > 60 ms in relation to the initial value [8].

A decrease of the left ventricular ejection fraction ≥ grade 3 according to CTCAE (i.e. when the left ventricular ejection fraction is < 40% or is decreased by > 20% in relation to the initial value) was observed in 4% patients treated with dabrafenib and trametinib, in 2% of those treated with vemurafenib and cobimetinib, and in 1% of those treated with encorafenib and binimetinib. Patients with cardiovascular diseases in their history should be prudently qualified for treatment with BRAF and MEK inhibitors, and during treatment the left ventricular ejection fraction, the troponin level, NT-proBNP, and CPK should be monitored. A decrease in the cardiac ejection fraction by > 10% is a reason for interrupting treatment, and > 20% for stopping it. In symptomatic patients, introducing a beta-blocker can be considered [8].

Hypertension can also be caused by BRAFi and MEKi. During treatment with dabrafenib and trametinib this problem concerns 29% patients, vemurafenib and cobimetinib 16%, and encorafenib and binimetinib 11%. In this case, hypotensive treatment should be initiated according to the guidelines in force [8].

Recommendations concerning procedures in the case of clinically significant adverse effects of BRAFi + MEKi therapy are presented in Table 3 [8].

Table 3. Recommended actions for selected adverse effects of BRAFi MEKi therapy [8]

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Dermatological complications				
Rash	Hydrating creams, continuation of treatment with inhibitors	Topical corticosteroids (in case of maculopapular rash), topical antibiotics (for papular rash), continuation of treatment with inhibitors	Dermatological consultation, reduction of inhibitor doses	Termination of treatment, hospitalization, if e.g. Stevens-Johnson syndrome occurs, toxic epidermal necrolysis
Hypersensitivity to light	Patient education, UV50 protective creams, protection from sun, topical glucocorticosteroids; continuation of treatment with inhibitors	As for grade 1	Dermatological consultation, reduction of inhibitor doses	Dermatological consultation, stopping treatment with inhibitors considered
Hand and foot keratosis	Patient education, urea creams, topical glucocorticosteroids; continuation of treatment with inhibitors	As for grade 1	Dermatological consultation, reduction of inhibitor doses; stopping treatment with inhibitors considered	This adverse effect has not been reported at grade 4
Gastrointestinal complications				
Diarrhoea	Loperamide/octreotide; continuation of treatment with inhibitors	As for grade 1, reduction of inhibitor dose recommended	As for grade 1, inhibitor dose reduction required	Stopping treatment with inhibitors considered
Nausea and vomiting	Pharmacological prophylaxis (available anti-emetic drugs, corticosteroids); continuation of treatment with inhibitors	As for grade 1, dose reduction can be considered	As for grade 1, inhibitor dose reduction required	Stopping treatment with inhibitors considered
Hepatotoxicity	Continuation of treatment with inhibitors	Dose reduction can be considered	Hepatologist consultation recommended; inhibitor dose reduction required	Stopping treatment with inhibitors considered
General symptoms				
Fever	Antipyretic drugs, corticosteroids, interruption of inhibitor treatment if > 38.5°C	As for grade 1, reduction of inhibitor dose recommended especially in case of recurring fever	inhibitor dose reduction required	Stopping treatment with inhibitors considered
Adverse events in the musculoskeletal system				
Joint pain	NSAIDs, continuation of treatment with inhibitors	As for grade 1, dose reduction can be considered	Rheumatologist consultation, inhibitor dose reduction required; stopping treatment with inhibitors considered	This adverse effect has not been reported at grade 4
Muscle pain	Continuation of treatment with inhibitors	As for grade 1, dose reduction can be considered	Rheumatologist consultation, inhibitor dose reduction required; stopping treatment with inhibitors considered	This adverse effect has not been reported at grade 4
Cardiovascular complications				
Arterial hypertension	Self-control, hypotensive treatment according to standards in force, continuation of treatment with inhibitors	As for grade 1, dose reduction can be considered	As for grade 1, inhibitor dose reduction required	Stopping treatment with inhibitors considered

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Table 3. cont. Recommended actions for selected adverse effects of BRAFi MEKi therapy [8]

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4
Left ventricle dysfunction	This adverse effect has not been reported at grade 1	Cardiologist consultation; dose reduction can be considered	Cardiologist consultation, inhibitor dose reduction required or stopping treatment	Cardiologist consultation, stop treatment with inhibitors
QT prolongation	Modification of cardiological treatment, equilibration of hydro-electrolyte perturbations, continuation of treatment with inhibitors	Cardiologist consultation; dose reduction can be considered	Cardiologist consultation, inhibitor dose reduction required or stopping treatment	Cardiologist consultation, stop treatment with inhibitors
Eye complications				
Central serous retinopathy	continuation of treatment with inhibitors	Dose reduction can be considered	Ophthalmologist consultation, inhibitor dose reduction required	Ophthalmologist consultation, stopping treatment with inhibitors considered
Kidney derived complications				
Acute kidney damage with increase in creatinine	Continuation of treatment with inhibitors	Irrigation, exclusion of other causes, dose reduction can be considered	Nephrologist consultation, inhibitor dose reduction required	Nephrologist consultation, stop treatment with inhibitors
Lung complications				
Pneumonia	Continuation of treatment with inhibitors	If symptomatic, corticosteroids, dose reduction can be considered	Pulmonologist consultation, inhibitor dose reduction required or stopping treatment	Pulmonologist consultation, stop treatment with inhibitors

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VIA MEDICA

CASE REPORT

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Long-term complete remission of pancreatic cancer after first-line chemotherapy with gemcitabine and nab-paclitaxel in a patient with depressive disorder

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ABSTRACT

The article presents the case of a 64-year-old pancreatic cancer patient with complete remission of hepatic metastases after first-line chemotherapy with gemcitabine and nab-paclitaxel. Partial regression of metastatic tumours in the liver was achieved after three months of therapy, and after three more months complete remission was achieved. Grade 4 neutropaenia was reported once during the treatment. The patient was temporarily reluctant to start treatment. Better cooperation was achieved after using psychotherapy. The following case confirms the impact of the patient's mental condition on the treatmentinitiation. The possibility of obtaining long-term complete remission in advanced pancreatic cancer — a disease with poor prognosis — following the use of gemcitabine and nab-paclitaxel-containing chemotherapy is documented.

Key words: complete response, pancreatic cancer, gemcitabine, nab-paclitaxel, depression

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Introduction

Pancreatic cancer is a solid tumour with a very poor prognosis, in which the mortality is almost equal to the incidence, and less than 5% of patients survive five or more years. The only method of radical treatment is surgical resection. Unfortunately, due to the high biological and clinical tumour aggressiveness and lack of early symptoms, the cancer is usually diagnosed at a very advanced stage. In about 80% of patients after radical treatment relapse occurs within the first three years after diagnosis and the choice of appropriate chemotherapy is important to achieve maximum survival in metastatic pancreatic cancer [1]. For many years 5-fluorouracil was the standard of treatment for stage IV of the disease. Progress was associated with the introduction of gemcitabine — the results of a study by Burris et al. [2] showed the possibility of extending overall survival (OS) by 1.3 months compared to 5-fluorouracil.

The introduction of the multi-drug FOLFIRINOX regimen was important in the first-line treatment of patients with advanced pancreatic cancer. The results of the ACCORD 11/PRODIGE 4 phase III study, which compared the effectiveness of FOLFIRINOX with gemcitabine, showed prolongation of median OS, progression-free survival (PFS), and one-year survival rate (11.1 *vs.* 6.4 months; 6.8 *vs.* 3.3 months; 48% *vs.* 21%, respectively) [3]. Unfortunately, the FOLFIRINOX

regimen is toxic and only properly selected patients are able to tolerate it in full doses [4].

Recently, a new doublet chemotherapy regimen consisting of gemcitabine and nab-paclitaxel has been introduced into clinical practice [5]. In a multicentre phase III clinical study this doublet was superior to gemcitabine monotherapy in terms of OS (median 8.5 *vs.* 6.7 months; $P < 0.0001$), PFS (5.5 *vs*. 3.7 months; $P < 0.0001$) and the objective response rate (ORR) (23% *vs*. 7%). The aforementioned doublet is an important first-line treatment option in patients with metastatic pancreatic cancer because it is less toxic than the FOLFIRINOX regimen and gives comparable results, an example of which is the presented clinical case.

Depression very often coexists with pancreatic adenocarcinoma. The incidence of so-called major depressive disorder (MDD) in pancreatic cancer reported in the literature is up to seven times higher than in the general population [6]. A meta-analysis of six prospective studies in pancreatic cancer estimates that 43% of patients experience depression after being diagnosed. Depression and loss of psychomotor drive represent a particularly adverse syndrome occurring in some patients with pancreatic cancer [7]. In such cases, patients give up taking treatment that could potentially prolong their life or significantly relieve the symptoms of cancer, because they feel too tired to make the effort and visit the oncology centre.

Depression accompanying pancreatic cancer is most commonly diagnosed in patients over 65 years of age, who are not working, and it usually occurs within the first three months after surgery or in patients without the possibility of surgical intervention [8].

Case report

On January 2, 2017, a 64-year-old female patient underwent pancreatoduodenectomy for carcinoma of the *head* of the *pancreas*. Histopathological examination revealed pancreatic ductal adenocarcinoma (presence of necrosis, G2 malignancy, complete resection, pT2N1 stage, metastases in 2 out of 10 examined lymph nodes, features of vascular invasion). Computed tomography of the chest, abdominal cavity, and pelvis performed before the surgery did not reveal distant metastases. One month after surgery, CA19.9 and CEA levels were 87.7 IU/mL and 1.6 ng/mL, respectively. The result of the examination together with planned adjuvant treatment and prognosis were discussed with the patient. The patient refused the proposed treatment despite detailed information. She did not have a psycho-oncologist consultation. Three years before the diagnosis she had an episode of depression related to the sudden death of her daughter (no detailed medical documentation).

After six months, at the instigation of the family, the patient went to an oncologist in another centre. The level of CA19.9 and CEA markers were 484.6 IU/mL and 4.4 ng/mL, respectively. A CT scan of the chest, abdomen, and pelvis was performed on June 6, 2017 (Fig. 1A). Based on the examination, numerous metastatic lesions were found in both liver lobes with diameters of up to 13 mm. A portocaval node (17 x 9 mm) was described in the hilum of the liver close to the celiac trunk. The result was compared to the examination from December 30, 2016, and progression of the disease in the liver was diagnosed (Fig. 2). The results of blood and biochemical morphology were within normal range.

On July 5, 2017, the patient decided to start palliative chemotherapy. She received nab-paclitaxel at a dose of 125 mg/m^2 with gemcitabine at a dose of 1000 mg/m^2 on days 1, 8, and 15 every 28 days. After administration of the first part of cycle 1, the values of white blood cells, neutrophils, and platelets were 2.98 G/L, 1.25 G/L, and 162 G/L, respectively. Filgrastim was given at a dose of 48 million units subcutaneously for three days. Before administration of the second part of cycle 2, the values of white blood cells, neutrophils, and platelets were 21.17 G/L, 17.0 G/L, and 123 G/L, respectively. After chemotherapy administration filgrastim was reused at a dose of 48 million units for two days as a secondary prevention of neutropaenia. Hair loss occurred after the first cycle. The patient did not report nausea and vomiting or symptoms of neurotoxicity, and the performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale was 0. The patient used a psycho-oncologist consultation and undertook regular psychotherapy.

After cycle 3 grade 4 neutropaenia was found (neutrophil count 0.26 G/L), and the ECOG PS was 2. Neutropaenic fever was not observed. Filgrastim was given at a dose of 48 million units subcutaneously for five days, and the number of leukocytes and neutrophils was 54.55 G/L and 45.91 G/L, respectively. Due to asthaenia and neutropaenia, at the patient's request, computed tomography was performed only on October 3, 2017 (after the second part of cycle 3; Fig. 1B). A single residual lesion with a diameter of 8 mm was found in segment 8 of the liver and almost complete regression was described. After administration of the second part cycle 4, grade 2 thrombocytopaenia (70 G/L) was found and chemotherapy was postponed for seven days. Complete blood count (CBC) prior to the third part of cycle 4 showed a platelet count of 510 G/L. A CT scan performed on January 4, 2018 showed several hypertensive areas visible only in the arterial phase (probably indicative of perfusion disorders). The total remission was determined according to the RECIST 1.1 criteria. Serum marker values were within normal range (CA19.9 — 7.31, CEA — 1.24).

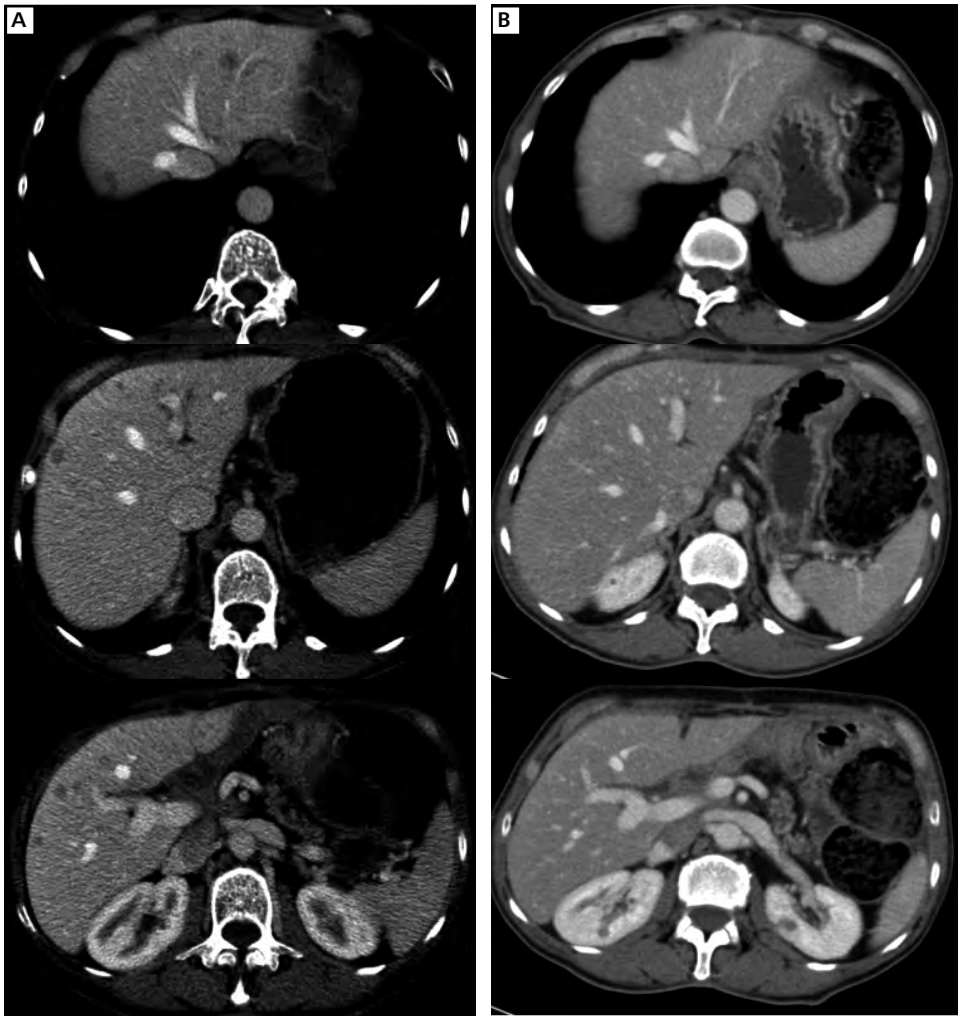

Figure 1. A. Computed tomography, 06.06.2017: numerous metastases in the liver; **B.** CT, 03.10.2017: complete regression

As per the patient's wishes and due to haematological toxicity, it was decided to discontinue chemotherapy and closely monitor the patient's state. Computed tomography performed on February 15, 2018 did not reveal metastatic changes or recurrence of the disease. Re-evaluation of serum markers on March 22, 2018 showed CA19.9 and CEA levels 7.08 IU/mL and 1.52 ng/mL, respectively. Computed tomography performed on April 13, 2018 and July 13, 2018 showed sustained complete remission. Marker levels were normal (CA19.9 — 6.8, CEA — 1.48), as was CBC. The patient gave up psychotherapy in June 2018 and took up her work.

A follow-up CT scan on November 15, 2018 showed complete remission, as did the last imaging test made on November 9, 2019. Marker levels were normal.

In 2019, the patient sporadically used the help of a psycho-oncologist. Complete remission of liver metastases lasts 24 months. Survival time from diagnosis is 36 months.

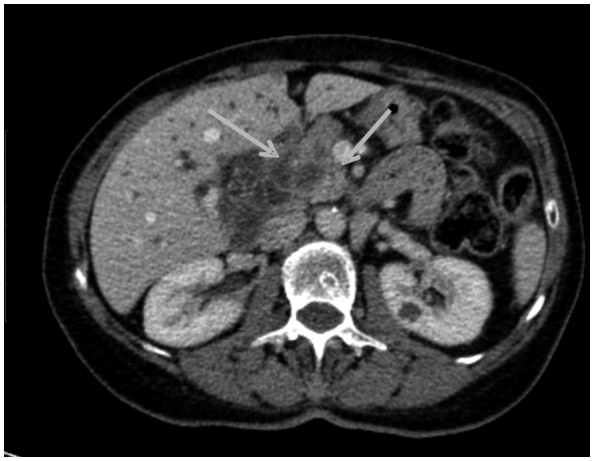

Figure 2. Computed tomography, 30.12.2016: tumour of the head of pancreas (↑↑), dilated bile ducts

Discussion

Improving the quality of life of cancer patients is an important issue for physicians, but it seems that mental disorders are much less frequently included in the history of the disease. The presented case of complete remission is undoubtedly a therapeutic success, but the perception of depressive symptoms and psychological therapy are of great importance in the entire recovery process.

There is evidence that in some patients the symptoms of mental disorders, especially depression, may precede the diagnosis of pancreatic adenocarcinoma by several or dozen months [9]. However, the authors of the cited publication agree that the diagnosis of depression and anxiety is not an indication for imaging tests for pancreatic cancer [10].

It is believed that high incidence of depression in patients with pancreatic cancer may be due to an increase in indolamine 2,3-dioxygenase, an enzyme in the kynurenine pathway that leads to a reduction in serotonin levels and the accumulation of cytotoxic metabolites in the brain [11]. Other reports, however, highlight the role of potentially common biomarkers for pancreatic cancer and depression, such as interleukin 6 (IL-6) or the *KRAS* gene [12].

The *KRAS* mutation is a well-validated factor stimulating the growth of pancreatic cancer cells. The significant importance of this biomarker in biological processes that lead to the appearance of depression has already been confirmed, especially in the population of patients over 65 years of age [12, 13]. In the described patient we did not assess the level of IL-6 and *KRAS* gene status due to the lack of patient consent.

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