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REVIEW ARTICLE

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Response assessment in cancer immunotherapy. Cooperation between the oncologist and the radiologist

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ABSTRACT

One of the paradigms of clinical oncology is systemic treatment on the condition that the patient obtains a therapeutic benefit. The evaluation of the benefit from treatment should be based on clinical premises together with a radiological evaluation of the response. Evidently, this implies the need for a collaboration between the clinician and the radiologist. The diversity of responses to treatment, in particular, the occurrence of the so-called atypical responses to immunotherapy requires strict cooperation between clinicians and radiologists.

Key words: criteria of response evaluation, immunotherapy, pseudoprogression, atypical response

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Significance of response evaluation in oncology

One of the paradigms in clinical oncology is systemic treatment on the condition that the patient obtains a therapeutic benefit [1]. In the case of the metastatic disease this can be measured by the prolongation of the progression-free time, obtaining a response (which is of fundamental importance in symptomatic patients, in whom a decrease in tumor mass may lead to a decrease of the intensity of symptoms), or — the most desirable — a prolongation of the overall survival time [2]. At the same time the potential undesirable effects of a given therapy, which can negatively affect the patient's quality of life, should be kept in mind. The evaluation of the treatment benefits should be based on clinical premises, such as the performance status, intensity of symptoms or the need for analgesic drugs, together with a radiological evaluation of the response. This evidently implies the need for cooperation between the clinician and the radiologist, who should have access to the requisite clinical data concerning individual patients. They concern above all the histopathological diagnosis, the type of systemic treatment, the effects of previous treatment lines and their duration, the undergone surgical treatment or other forms of local treatment (particularly radiotherapy or ablation methods such as e.g. thermoablation). The next extremely important aspect is to provide the radiologist with the documentation of previously performed imaging tests if they were performed in another center. Only thus can the evolution of changes found in imaging studies be evaluated as well as the dynamics of the disease. The direct contact of the radiologist with the attending physician is also important.

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Immunotherapy in treating tumors on the example of renal cell carcinoma

Renal cell carcinoma (RCC) constitutes about 3% of malignant tumors [3]. In about 50% of patients, the disease is discovered accidentally during imaging tests of the abdominal cavity performed for other reasons [4]. In about 20% of patients with an RCC diagnosis synchronous distant metastases are detected and in a further 30%, this occurs during observation [4]. Clear cell renal cell carcinoma is a tumor which is resistant to treatment using cytostatics [5]. Cytokine-based immunotherapy — interleukin-2 or interferon alpha (IFN-α) turned out to be an effective form of treatment in selected groups of patients [6]. Interferon alpha has antiangiogenic, antiproliferative and immunomodulating activity. Immunotherapy using this cytokine was found to extend the median survival of RCC patients by 25 months in comparison with medroxyprogesterone [7]. The greatest benefits of this treatment were observed in patients with a favorable prognosis according to the Memorial Sloan Kettering Cancer Center (MSKCC) scale [8], with good performance status and with metastases limited to the lungs. Advances in molecular biology [9, 10] has led to the use in RCC treatment of drugs inhibiting angiogenesis — bevacizumab (anti-VEGF antibody) in combination with IFN-α [11, 12], multikinase inhibitors — sorafenib, sunitinib and pazopanib [13–15]. In the group with an unfavorable prognosis according to MSKCC temsirolimus was registered (mTOR inhibitor) [16]. Then the possibilities of second and successive treatment lines arose after the failure of antiangiogenic treatment. For this indication, an mTOR inhibitor (everolimus) [17] and next-generation multikinase inhibitors — axitinib [18] and cabozantinib (also inhibiting MET and AXL kinases) [19] were registered. Basic research allowing a better understanding of immunological mechanisms led to the elaboration of drugs from the group of immune checkpoint inhibitors (ICI). They affect the regulation of lymphocyte activation, differentiation and also inhibition of their apoptosis [20]. In phase III clinical trials in RCC patients ICI was found to be effective in monotherapy [21], a combination of anti-PD-1 and anti-CTLA4 antibodies [22, 23], and also in combined therapy of ICI z with a multikinase inhibitor [24, 25].

The European Medicines Agency (EMA) has registered the following drugs for treating metastatic renal cell carcinoma: nivolumab (anti-PD-1 antibody; in monotherapy or in combination with ipilimumab), ipilimumab (anti-CTLA4 antibody) in combination with nivolumab, avelumab (anti-PD-L1 antibody) in combination with axitinib and pembrolizumab (anti-PD-1 antibody) in combination with axitinib.

The use of immunotherapy in treating patients with clear cell renal cell carcinoma is recommended by scientific societies in first-line treatment [combined ICI/ICI therapy in the group with intermediate and unfavorable prognosis according to the International Metastatic RCC Database Consortium (IMDC) and TKI-VEGFR/ICI regardless of the prognosis] and in second or third-line treatment (ICI monotherapy) [26, 27].

In Poland currently only nivolumab is reimbursed as second-line treatment, used after failure of earlier antiangiogenic treatment using a multikinase inhibitor. Nivolumab for this indication was registered on the basis of the CheckMate 025 trial [21]. This was a randomized phase III trial in which patients after one or two lines of antiangiogenic treatment were randomized (at a 1:1 ratio) to immunotherapy with nivolumab (3 mg/kg body weight) or molecularly targeted treatment with the mTOR inhibitor — everolimus (10 mg/d.). During the 2020 Genitourinary Cancers Symposium organized under the auspices of the American Society of Clinical Oncology (ASCO) the final results of this trial were presented (after 60 months of follow-up). Median overall survival in the group of patients receiving immunotherapy was 25.8 months (95% CI 22.2–29.8) *vs.* 19.7 months (95% CI 17.6–22.1) in the control arm, the hazard ratio (HR) of death was 0.73; $p < 0.0001$. Median progression-free survival was 4.2 months *vs.* 4.5 months, respectively, HR for progression 0.84 (0.72–0.99), $p = 0.03$. Responses were evaluated on the basis of RECIST 1.1 (Response Evaluation Criteria In Solid Tumors). Objective responses were found in 23% *vs.* 4% patients. Progression as the best response was found in 35% of patients treated with nivolumab and in 26% receiving everolimus. According to the protocol continuation of the treatment after progression was allowed if patient derived benefit. Taking into consideration the possibility of occurrence of the pseudoprogression phenomenon, this is an extremely important aspect, as in this situation treament termination based on only on the basis of observing progression in imaging studies could deprive the patient of the effects of the treatment. In this context, the evaluation of the clinical state of the patient receiving immunotherapy is of particular importance. In the case of pseudoprogression the patient's status, in general, remains stable whereas in the case of real progression it worsens [28].

Radiological response evaluation criteria in oncology

An objective evaluation of the response to treatment (regardless of clinical data) is possible on the basis of imaging studies. The first criteria introduced in 1979 were those of the World Health Organization (WHO) (Miller et al. [29]). Many radiological methods of evaluation appeared in successive years, among

them the RECIST criteria are commonly accepted in everyday practice and in clinical trials. These criteria published in 2000 and then modified in 2009 [30] as version 1.1 are still in force in the evaluation of standard cytotoxic therapies used in the treatment of most solid tumors. There are many papers on this subject (i.a. Płużański [31]), to which the interested reader may refer. However, the basic principles on which these criteria are based should be underlined. These are anatomical criteria, evaluating exclusively the size of the leasions (primary tumor and/or metastases). Computed tomography (CT) it the preferred imaging method for evaluation in RECIST 1.1 but in some cases, MR is also used. One linear dimension of the tumor is measured (the largest perpendicular dimension or the size of the short axis in the case of lymph nodes). RECIST criteria define measurable and non-measurable lesions in a precise fashion. Among the former target, lesions are selected. The remaining lesions (both measurable and non-measurable) are non-target lesions. We propose using these terms which have been accepted in everyday practice and are better at conveying their meaning than the terms „addressed and non-addressed lesions", sometimes used in the literature. RECIST criteria assume 4 response categories: complete regression, partial regression, stabilization and disease progression. It is worth stressing that the interpretation (radiological description) of a successive CT analysis performed during treatment should finish with the conclusion to which category of response this analysis can be qualified. The decision about continuing or interrupting the treatment should, of course, be made by the oncologist on the basis of the whole clinical picture and additional analyses, but it is the radiologist who must provide precise information derived from imaging studies.

Critical evaluation of disease progression

The radiologist has a particular responsibility if the progression of the disease is suspected (on the basis of the evaluation of imaging studies). RECIST 1.1. criteria use the following definitions of disease progression [30]:

— an increase of the sum of target lesions by 20% or more (at least 5 mm in absolute values) in relation to the examination in which this sum was the smallest (nadir) and/or
— the appearance or one or more new lesions and/or
— evident (not doubtful) increase in the size of non-target lesions.

It is very important to compare the current examination not only with the previous one but also with earlier analyses: the initial one and (this is key for detecting disease progression) with the examination in which the sum of the dimensions was the smallest (nadir).

If new lesions appear it is important to be certain that they represent symptoms of malignancy. For instance, the appearance of (or increase of the volume of) fluid in the pleural or peritoneal cavity may be a symptom of a reaction to treatment (inflammatory reaction, fluid retention in the organism), and not the disease itself [32, 33].

In turn, the appearance of blastic (sclerotic) foci observed in successive CT analyses during the treatment most commonly indicates an osteoblastic reaction (calcification of metastatic foci in bone marrow, not visible in previous CT analyses) and cannot be treated as a symptom of disease progression – on the contrary, it is a beneficial reaction to treatment [34] (Fig. 1). The examples given above require particular attention during the interpretation of imaging studies and should be appropriately described and evaluated, together with the clinical status of the patient.

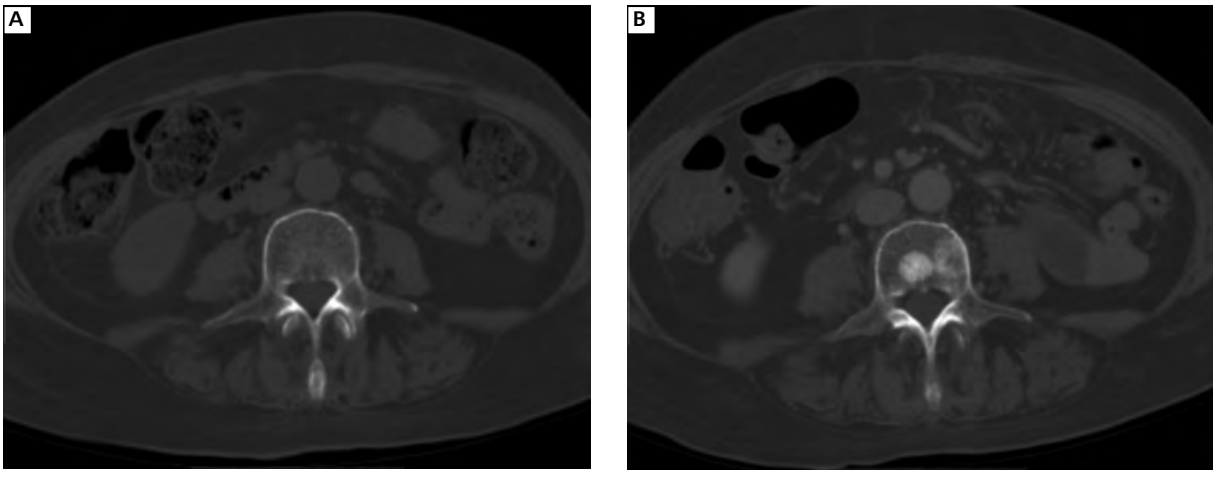

Figure 1. Osteoblastic reaction. CT analysis in a patient with non-small cell lung cancer during chemotherapy. (**A**) image before initiation of treatment — no lesions in bones visible; (**B**) image after a successive cycle of chemotherapy — appearance of blastic foci in the vertebral body corresponds to calcification of metastases which were present but not visible in the initial TK examination

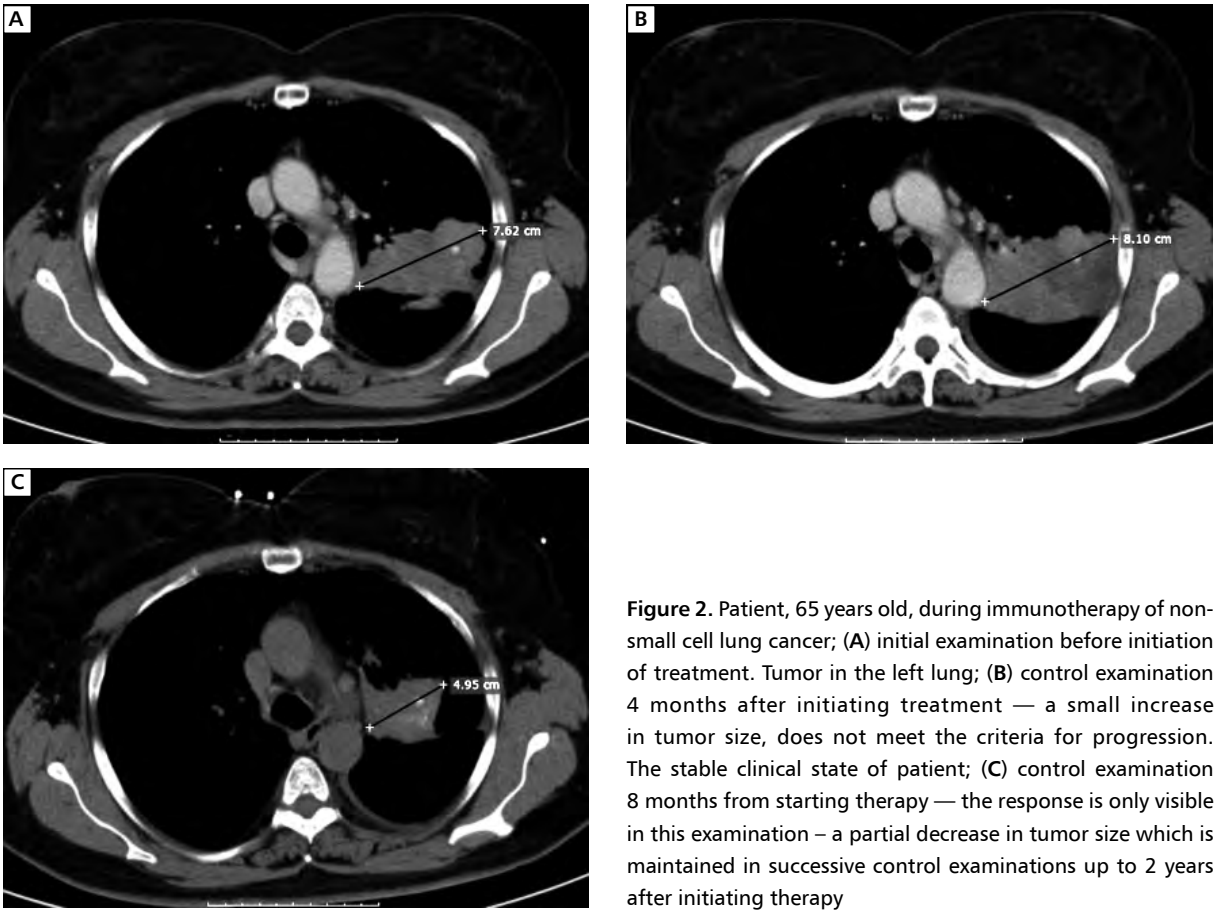

Figure 2. Patient, 65 years old, during immunotherapy of non-small cell lung cancer; (**A**) initial examination before initiation of treatment. Tumor in the left lung; (**B**) control examination 4 months after initiating treatment — a small increase in tumor size, does not meet the criteria for progression. The stable clinical state of patient; (**C**) control examination 8 months from starting therapy — the response is only visible in this examination – a partial decrease in tumor size which is maintained in successive control examinations up to 2 years after initiating therapy

Evaluation of response immunotherapy. New response criteria(irRC, irRECIST, iRECIST)

RECIST criteria were elaborated and introduced into common usage in 2000, thus during the period when cytostatic drugs were the basis of chemotherapy in oncology. The development of new therapies, especially the increasingly frequent use of immunotherapy, gives rise to the question of whether these criteria are reliable to evaluate the response in new types of therapy. Since immunotherapy is based on a completely different mechanism of action than standard cytotoxic therapies, different responses to treatment can be expected than those which have been observed so far. A reaction to treatment may occur (and be observed in imaging studies) with a longer delay, sometimes lasting even up to several months after initiating treatment (Fig. 2). It can also be maintained longer, even after termination of the treatment [35].

Atypical reactions

Reactions have been also observed which did not occur during standard therapies. The phenomenon of pseudoprogression should particularly be mentioned. This is based on the initial increase in the size of the lesions and/or the appearance of new lesions after initiating treatment, and then subsequent decrease in the further course of therapy (Fig. 3). This phenomenon was observed for the first time during immunotherapy of patients with metastatic melanoma, and subsequently during the therapy of other malignancies [36].

The mechanism of the increase in the size of the tumor or metastases can be explained by infiltration by the immune cells (mainly T lymphocytes) of the tumor, which leads to a transient increase of its volume visible in imaging studies or clinical examinations. This has been confirmed in histopathological analyses of resected melanoma lung metastases. Lesions invisible in the initial examination (because they were too small) can appear in the course of immunotherapy also because of their transient increase in size (immune infiltration and necrosis within the tumor) which makes them visible in imaging studies (Fig. 4). In the case of pseudoprogression, this increase in size is not caused by an increase in the number of cancer cells which distinguishes this phenomenon from true progression.

The frequency of pseudoprogression for metastatic melanoma attains 10% of patients observed during immunotherapy [37]. In non-small cell lung cancer it is

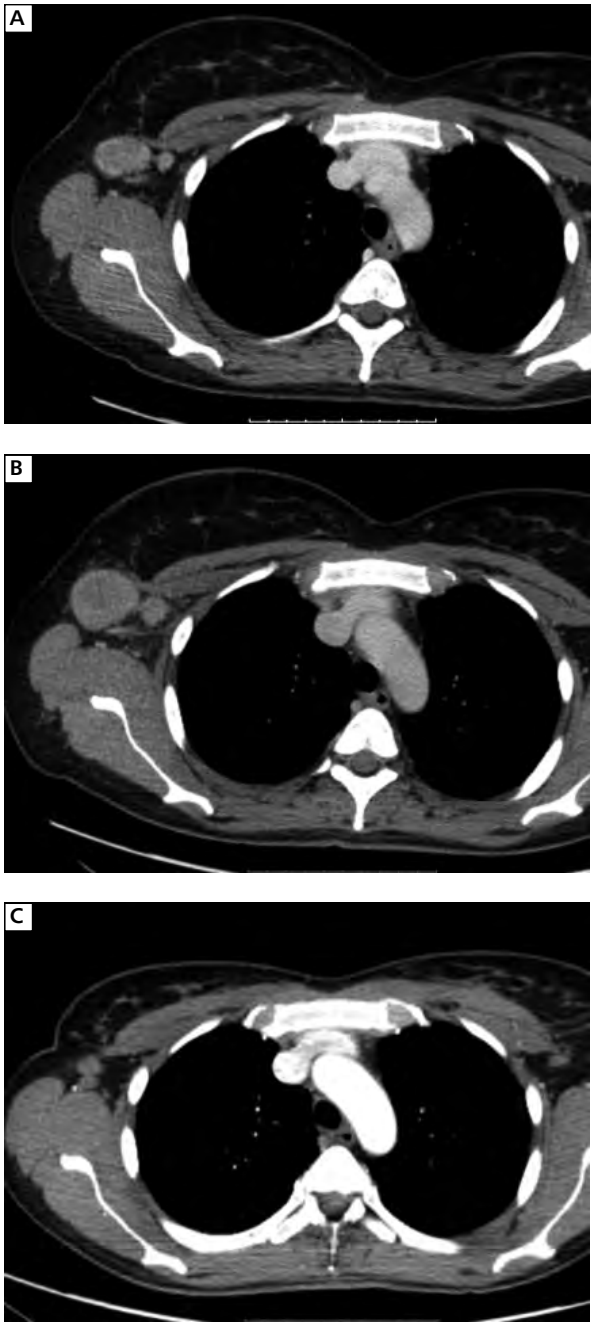

Figure 3. The pseudoprogression phenomenon. Woman, 30 years old, with metastatic melanoma of trunk skin; (**A**) initial examination — enlarged right axillar node (target lesion); (**B**) the first scan after the initiation of immunotherapy — clear increase in size, meets progression criteria (RECIST 1.1.); (**C**) CT scan after 2 successive cycles of immunotherapy — clear decrease of the size of the lymph node to normal dimensions — complete regression

less frequent — up to 5% [38]. The frequency of this phenomenon during immunotherapy of other malignancies is not known and requires further observations. The phenomenon of pseudoprogression during immunotherapy, though infrequent, can be a cause of diagnostic errors, which lead to premature termination of treatment. Hence proposals have appeared during clinical trials not to interrupt treatment after progression is observed in imaging studies if the clinical status of the patient is stable. This phenomenon has also been the basis of different criteria for evaluating response in immunotherapy.

Hyperprogression is a second very important atypical phenomenon. This phenomenon described relatively recently in the course of immunotherapy [39] describes a sudden increase in tumor size after initiating therapy. The tumor growth rate (TGR) is important here as it can rapidly accelerate after applying immunotherapy, which is associated with a clear deterioration of the patient's status. An over twofold increase in TGR in the last examination in comparison with the tumor growth rate in previous examinations suggests hyperprogression. This aggressive and unfavorable mechanism of response to immunotherapy has been described in 9% of patients treated for various types of malignancies (Fig. 5).

The next type of atypical response to immunotherapy is a dissociated response (Fig. 6). It occurs in case when during treatment some of the lesions become smaller, and some larger [40]. So far this phenomenon has been poorly described. There are no precise definitions of how to detect it and what criteria should be used in imaging studies in this situation. Tazdait et al. observed this type of response in 7.5% of patients with non-small cell lung cancer during immunotherapy and associated it with better survival than in the group of patients with real progression [41]. The possibility of using radiotherapy in selected cases for foci which increase in size during immunotherapy (e.g. metastases in the brain or bones) with a good response to treatment and an increase in overall survival was pointed out [42].

Criteria of response evaluation to immunotherapy

Different response evaluation criteria have been proposed for immunotherapy, which takes into consideration atypical reactions to treatment. The first proposal was criteria elaborated for evaluation of immunotherapy of metastatic melanoma [36]. These criteria called immune-related response criteria (irRC) were based on WHO criteria. They are two-dimensional criteria (two dimensions of the lesion size) in which the sum of the products of perpendicular sizes of lesions which are considered as targets is evaluated. If new lesions appear their dimensions are added to the sum of the dimensions of the measured lesions. Progression is defined as an increase in the sum of the lesion dimensions ≥ 25%. It

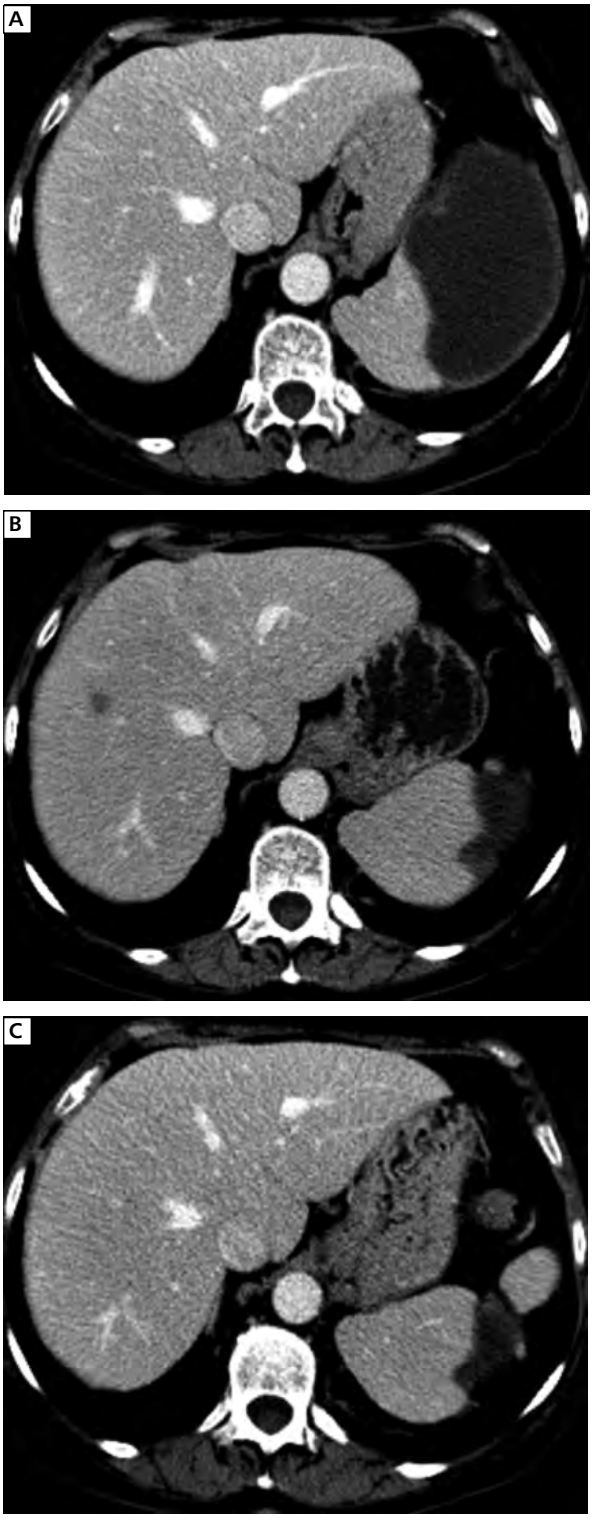

Figure 4. Pseudoprogression phenomenon — the appearance of new foci. Woman, 75 years old, with non-small cell lung cancer; (**A**) initial examination before starting immunotherapy — normal appearance of the liver; (**B**) first control examination during immunotherapy. A focus with the appearance of metastasis has appeared in the liver; (**C**) next control examination — the focus has undergone complete regression

is indispensable to confirm the increase in lesion size in a control examination performed not earlier than 4 weeks after the recent examination. This method of measurement allows the continuation of treatment even if progression criteria are fulfilled in examination studies in the absence of clinical symptoms of disease progression. Only the confirmation of the increase in the dimensions of the lesions ≥ 25% in two successive examinations can be the basis for stopping the treatment.

irRECIST criteria. The next proposal for evaluating immunotherapy were criteria based on RECIST 1.1. principles (one-dimensional, evaluating the sum of the largest sizes of the target lesions), but maintaining basic irRC principles if disease progression (PD, *progressive disease*) was suspected. These criteria, described as immune-related RECIST (irRECIST), require confirmation of PD in two successive control examinations and include the dimensions of new measurable lesions into the total sum of target lesions. They were introduced in 2013 [43] in clinical trials of new immunotherapy drugs. These authors demonstrated the high agreement of irRECIST and irRC criteria in response evaluation in a group of patients with advanced melanoma, however, irRECIST criteria were characterized by better reproducibility which allows comparison of treatment effectiveness with earlier clinical trials, where methodology was based on standard RECIST 1.1. criteria [43]. It is also worth underlining that these criteria are simpler and less time-consuming to use than irRC.

iRECIST criteria. One of the last proposals are criteria elaborated for the requirements of immunotherapy by the RECIST working group [44]. They are based on RECIST 1.1. principles concerning the measurements and selection of target and non-target lesions, but they introduce modifications in order to adapt the response evaluation to atypical reactions encountered in immunotherapy. The concept of immune unconfirmed progressive disease (iUPD) is introduced; this requires confirmation in a control examination performed during the next 4–8 weeks. iUPD is based on RECIST 1.1. principles, but confirmed progression (iCPD, immune confirmed progressive disease) occurs in the situation when in the next control examination additional new lesions appear or previously observed new lesions become larger, or the sum of the target lesions increases by an additional size ≥ 5 mm or (qualitatively evaluated) any increase of the size of non-target lesions is observed. If this does not happen the result of the examination is still described as unconfirmed progression and treatment is continued (in correlation with the clinical picture). It should be stressed that a small increase in the sum of target lesions (≥ 5mm) or any increase in the size of non-target lesions is sufficient to confirm disease progression. Detailed principles of using iRECIST criteria are given on the

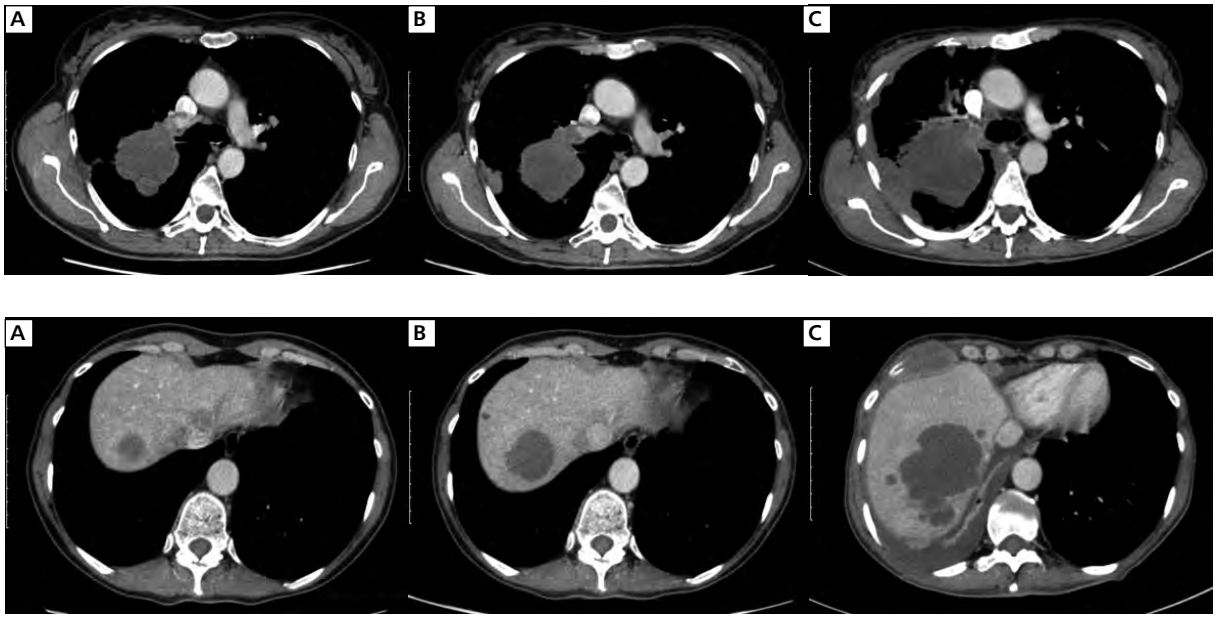

Figure 5. Hyperprogression. Woman, 54 years old, diagnosed with non-small cell lung cancer; (**A**) examination during chemotherapy — lung tumor (upper row) and liver metastases (lower row); (**B**) disease progression was observed during the next examination (increase in the size of liver metastases). Immunotherapy was initiated; (**C**) first control examination during immunotherapy — a considerable increase in the size of the lung tumor and liver metastases. New metastases have appeared in the pleura and bones. Clear deterioration of the patient's status

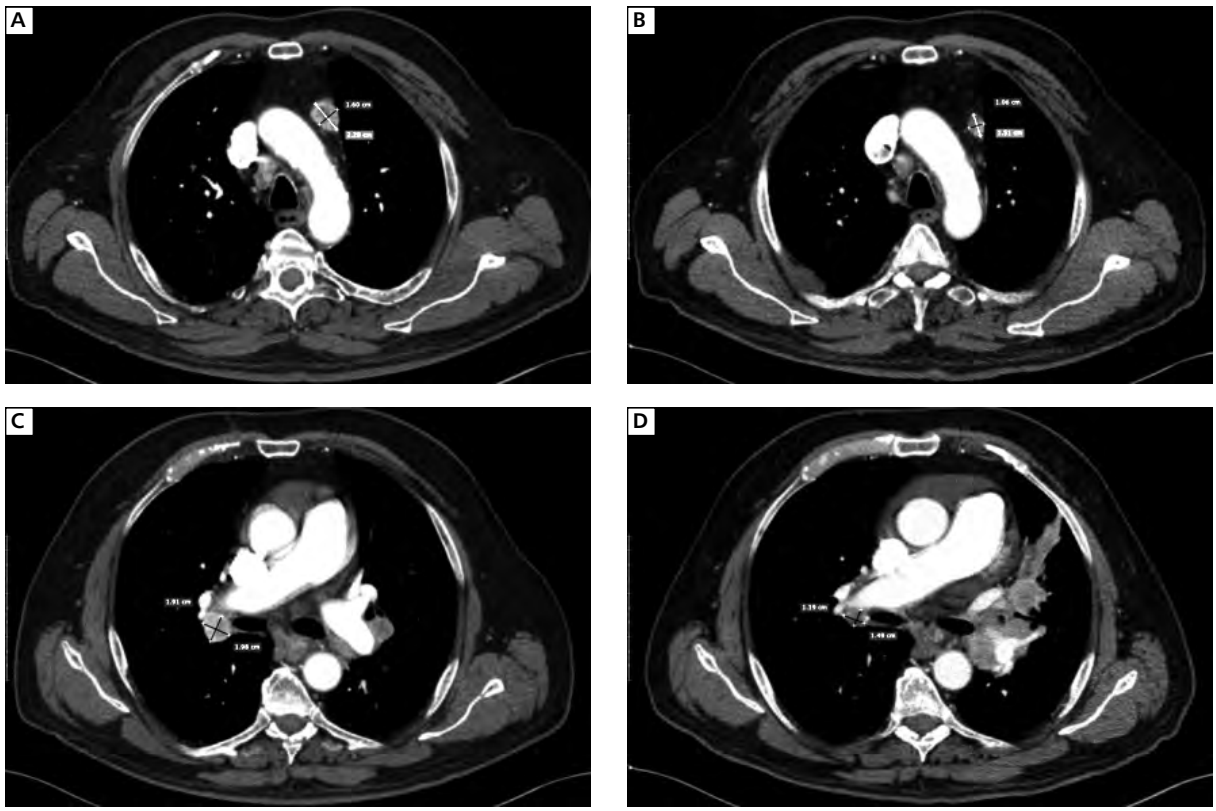

Figure 6. Example of a dissociated response. Man, 60 years old, in the course of immunotherapy for metastatic clear cell renal cell carcinoma carcinoma. Left side (**A**, **C**) — CT scan before initiating treatment. Enlarged mediastinum and internal right and left lung lymph nodes. Right side (**B**, **D**) — CT scan after initiating immunotherapy. A clear decrease in size of the mediastinum and internal right lung nodes with a simultaneous increase in the size of the internal right lung lymph nodes

web page https://recist.eortc.org/irecist/. irRECIST and iRECIST criteria are based on RECIST 1.1. criteria and the difference consists in the evaluation in the case of suspected disease progression. All of them — irRC, irRECIST as well as iRECIST require a subsequent imaging examination performed after 4–8 weeks in order to confirm disease progression.

The criteria for evaluating response to immunotherapy described above are applied mainly in clinical trials. They have not yet been introduced into everyday clinical practice nor into drug reimbursement programs. The increasing frequency of therapies based on checkpoint inhibitors gives rise to the risk of an incorrect evaluation of response to treatment with strict adherence to RECIST 1.1. principles. Most drug reimbursement programs are based on RECIST 1.1. criteria. If an increase in the size of the target lesions occurs (fulfilling progression criteria) or new lesions appear such a result of the examination obligatorily causes an interruption of treatment. There is a high probability that in some of the patients' interruption of treatment is premature and may exclude them from a therapy which could lead to improved survival. The radiologist performs the examination in an objective fashion in agreement with the principles and provides the oncologist with information on the basis of which he makes a decision. Observation of disease progression in CT imaging currently does not require its confirmation in a subsequent control examination which excludes the possibility of verifying what is the real effect of the treatment. The aim should be to change the Polish National Drug Reimbursement Program Guidelines, in a fashion taking into consideration the possibility of atypical reactions in the course of immunotherapy and allow the continuation of treatment until an examination confirming or excluding progression can be performed after 4–8 weeks.

Analysis of imaging studies (CT) should be performed by radiologists familiar with the response evaluation criteria in oncology and experienced in their application. The evaluation of subsequent control examinations is necessary, together with the initial examination. It is important to determine the examination in which the sum of the target lesions is the smallest (nadir), this will be the basis for the eventual evaluation of disease progression. A situation when the current examination is only compared with the previous one is inadmissible.

The radiologist evaluating the patient's results must know his basic clinical data, but also basic data concerning treatment (a type of treatment, the administered drug, when was the therapy started, undergone surgeries and other types of treatment). The constant collaboration between the oncologist and the radiologist is indispensable. Similarly, as radiologists should be required to be able to apply treatment response evaluation criteria, oncologists should be required to include basic clinical information in the referral to imaging studies and the possibility of contacting them directly if there are any suspicions during the interpretation of the result. Situations (unfortunately frequent) are inadmissible when the referral only contains the patient's name and the statistical number of the disease. At the same time, the oncologist referring the patient to examination in the course of treatment (marking on the referral that the description should be according to RECIST 1.1. criteria) should obtain an interpretation of the image and a final conclusion — to which category of response does the result of this examination belong. The increasingly frequent use of advanced therapies, in which evaluation of the response is based on objective information provided by imaging studies, requires the use of a "common language" understandable for oncologists and radiologists. RECIST criteria and their modifications (especially used in immunotherapy) can and should be such a language. To attain this a strict cooperation between oncologists and radiologists is required — especially in the frame of scientific societies, joint conferences and workshops.

Conflict of interest

Authors declare that they have no conflict of interest.

References

1. Krzakowski M, Wyrwicz L. Leczenie systemowe. In: Krzakowski M, Potemski P, Warzocha K, Wysocki P (ed.). Onkologia Kliniczna. Tom I. Via Medica, Gdańsk. 2014: 107–134.
2. Płużański A, Sacha T. Ocena wartości przeciwnowotworowego leczenia. In: Krzakowski M, Potemski P, Warzocha K, Wysocki P (ed.). Onkologia Kliniczna. Tom I. Via Medica, Gdańsk. 2014: 400–411.
3. Gupta K, Miller JD, Li JZ, et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev. 2008; 34(3): 193–205, doi: 10.1016/j.ctrv.2007.12.001, indexed in Pubmed: 18313224.
4. Pantuck A, Zisman A, Rauch M, et al. Incidental renal tumors. Urology. 2000; 56(2): 190–196, doi: 10.1016/s0090-4295(00)00655-5.
5. Makhov P, Joshi S, Ghatalia P, et al. Resistance to Systemic Therapies in Clear Cell Renal Cell Carcinoma: Mechanisms and Management Strategies. Mol Cancer Ther. 2018; 17(7): 1355–1364, doi: 10.1158/1535-7163.MCT-17-1299, indexed in Pubmed: 29967214.
6. Rini BI, Battle D, Figlin RA, et al. Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of renal cell carcinoma. J Immunother Cancer. 2016; 4(1): 81, doi: 10.1186/s40425-016-0180-7, indexed in Pubmed: 27891227.
7. Interferon-alpha and survival in metastatic renal carcinoma: early results of a randomised controlled trial. Medical Research Council Renal Cancer Collaborators. Lancet. 1999; 353(9146): 14–17, indexed in Pubmed: 10023944.
8. Motzer RJ, Mazumdar M, Bacik J, et al. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol. 1999; 17(8): 2530–2540, doi: 10.1200/JCO.1999.17.8.2530, indexed in Pubmed: 10561319.
9. Mittal K, Koon H, Elson P, et al. Dual VEGF/VEGFR inhibition in advanced solid malignancies: clinical effects and pharmacodynamic biomarkers. Cancer Biol Ther. 2014; 15(8): 975–981, doi: 10.4161/cbt.29187, indexed in Pubmed: 24842548.
10. Escudier B, Pluzanska A, Koralewski P, et al. AVOREN Trial investigators. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet.

2007; 370(9605): 2103–2111, doi: 10.1016/S0140-6736(07)61904-7, indexed in Pubmed: 18156031.
11. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010; 28(13): 2137–2143, doi: 10.1200/JCO.2009.26.5561, indexed in Pubmed: 20368558.
12. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol. 2009; 27(20): 3312–3318, doi: 10.1200/JCO.2008.19.5511, indexed in Pubmed: 19451442.
13. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009; 27(22): 3584–3590, doi: 10.1200/JCO.2008.20.1293, indexed in Pubmed: 19487381.
14. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010; 28(6): 1061–1068, doi: 10.1200/JCO.2009.23.9764, indexed in Pubmed: 20100962.
15. Hudes G, Carducci M, Tomczak P, et al. Global ARCC Trial. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007; 356(22): 2271–2281, doi: 10.1056/NEJMoa066838, indexed in Pubmed: 17538086.
16. Motzer R, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008; 372(9637): 449–456, doi: 10.1016/s0140-6736(08)61039-9.
17. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011; 378(9807): 1931–1939, doi: 10.1016/S0140-6736(11)61613-9, indexed in Pubmed: 22056247.
18. Choueiri TK, Escudier B, Powles T, et al. METEOR investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016; 17(7): 917–927, doi: 10.1016/S1470-2045(16)30107-3, indexed in Pubmed: 27279544.
19. Zitvogel L, Kroemer G. Targeting PD-1/PD-L1 interactions for cancer immunotherapy. Oncoimmunology. 2012; 1(8): 1223–1225, doi: 10.4161/onci.21335, indexed in Pubmed: 23243584.
20. Motzer RJ, Escudier B, McDermott DF, et al. CheckMate 025 Investigators. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015; 373(19): 1803–1813, doi: 10.1056/NEJMoa1510665, indexed in Pubmed: 26406148.
21. Motzer RJ, Tannir NM, McDermott DF, et al. CheckMate 214 Investigators. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018; 378(14): 1277–1290, doi: 10.1056/NEJMoa1712126, indexed in Pubmed: 29562145.
22. Motzer RJ, Rini BI, McDermott DF, et al. CheckMate 214 investigators. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol. 2019; 20(10): 1370–1385, doi: 10.1016/S1470-2045(19)30413-9, indexed in Pubmed: 31427204.
23. Rini BI, Plimack ER, Stus V, et al. KEYNOTE-426 Investigators. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019; 380(12): 1116–1127, doi: 10.1056/NEJMoa1816714, indexed in Pubmed: 30779529.
24. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019; 380(12): 1103–1115, doi: 10.1056/NEJMoa1816047, indexed in Pubmed: 30779531.
25. Escudier B, Porta C, Schmidinger M, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019; 30(5): 706–720, doi: 10.1093/annonc/mdz056, indexed in Pubmed: 30788497.
26. Albiges L, Powles T, Staehler M, et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibition Is the New Backbone in First-line Treatment of Metastatic Clear-cell Renal Cell Carcinoma. Eur Urol. 2019; 76(2): 151–156, doi: 10.1016/j.eururo.2019.05.022, indexed in Pubmed: 31151678.
27. Vrankar M, Unk M. Immune RECIST criteria and symptomatic pseudoprogression in non-small cell lung cancer patients treated with immunotherapy. Radiol Oncol. 2018; 52(4): 365–369, doi: 10.2478/raon-2018-0037, indexed in Pubmed: 30367809.
28. Miller AB, Hoogstraten B, Staquet M, et al. Reporting results of cancer treatment. Cancer. 1981; 47(1): 207–214, doi: 10.1002/1097-0142(19810101)47:1<207::aid-cncr2820470134>3.0.co;2-6, indexed in Pubmed: 7459811.
29. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45(2): 228–247, doi: 10.1016/j.ejca.2008.10.026, indexed in Pubmed: 19097774.
30. Płużański A. Kryteria oceny odpowiedzi na leczenie RECIST 1.1. Nowotwory. Journal of Oncology. 2014; 64(4): 331–335, doi: 10.5603/njo.2014.0055.
31. Kim WK, Shingare AB, Ramaiya NH, et al. Fluid Retention Associated with Imatinib Treatment in Patients with GIST. Korean J Radiol. 2015; 16(2): 304–313.
32. Howard SA, Krajewski KM, Thornton E, et al. Decade of molecular targeted therapy: abdominal manifestations of drug toxicities--what radiologists should know. AJR Am J Roentgenol. 2012; 199(1): 58–64, doi: 10.2214/AJR.11.7432, indexed in Pubmed: 22733894.
33. Stattaus J, Hahn S, Gauler T, et al. Osteoblastic response as a healing reaction to chemotherapy mimicking progressive disease in patients with small cell lung cancer. Eur Radiol. 2009; 19(1): 193–200, doi: 10.1007/s00330-008-1115-6, indexed in Pubmed: 18677488.
34. Dromain C, Beigelman C, Pozzessere C, et al. Imaging of tumour response to immunotherapy. Eur Radiol Exp. 2020; 4(1): 2, doi: 10.1186/s41747-019-0134-1, indexed in Pubmed: 31900689.
35. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009; 15(23): 7412–7420, doi: 10.1158/1078-0432.CCR-09-1624, indexed in Pubmed: 19934295.
36. Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. J Clin Oncol. 2016; 34(13): 1510–1517, doi: 10.1200/JCO.2015.64.0391, indexed in Pubmed: 26951310.
37. Gettinger SN, Horn L, Gandhi L, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol. 2015; 33(18): 2004–2012, doi: 10.1200/JCO.2014.58.3708, indexed in Pubmed: 25897158.
38. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive disease is a new pattern of progression in cancer patients treated by anti-PD-1/PD-L1. Clin Cancer Res. 2017; 23(8): 1920–1928, doi: 10.1158/1078-0432.CCR-16-1741, indexed in Pubmed: 27827313.
39. Borcoman E, Kanjanapan Y, Champiat S, et al. Novel patterns of response under immunotherapy. Ann Oncol. 2019; 30(3): 385–396, doi: 10.1093/annonc/mdz003, indexed in Pubmed: 30657859.
40. Tazdait M, Mezquita L, Lahmar J, et al. Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria. Eur J Cancer. 2018; 88: 38–47, doi: 10.1016/j.ejca.2017.10.017, indexed in Pubmed: 29182990.
41. Liniker E, Menzies AM, Kong BY, et al. Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma. Oncoimmunology. 2016; 5(9): e1214788, doi: 10.1080/2162402X.2016.1214788, indexed in Pubmed: 27757312.
42. Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013; 19(14): 3936–3943, doi: 10.1158/1078-0432.CCR-13-0895, indexed in Pubmed: 23743568.
43. Seymour L, Bogaerts J, Perrone A, et al. RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017; 18(3): e143–e152, doi: 10.1016/S1470-2045(17)30074-8, indexed in Pubmed: 28271869.