Radiological Monitoring of Modern Immunotherapy: A Novel Challenge for Interdisciplinary Patient Care

Radiologisches Monitoring von modernen Immuntherapien: Neue Herausforderung für die interdisziplinäre Zusammenarbeit

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ABSTRACT

Background Immunotherapy represents an effective therapeutic approach for many malignant diseases that were previously difficult to treat. However, since immunotherapy can lead to atypical therapy response patterns in the form of pseudo-progression or mixed responses and comprise an altered spectrum of adverse reactions, they present a new challenge for oncologic imaging. Detailed knowledge in this area is essential for oncologic clinical radiologists, since the radiological report is a cornerstone of response assessment, and increasingly influences therapy regimens and coverage by health insurances.

Method This white paper is based on an expert meeting in Frankfurt am Main and subsequent discussions between the authors. Based on the iRECIST criteria, it is intended to provide orientation for a response assessment of oncologic patients undergoing immunotherapy that can be applied in the clinical routine.

Results Radiological therapy monitoring outside clinical studies is subject to inherent limitations, but should be performed based on iRECIST criteria, according to the opinion of the expert panel. It should be taken into account that immunotherapies can in principle lead to pseudo-progression and autoimmunological side effects. Since radiological follow-up is currently the only method to accurately distinguish real progressive disease from pseudo-progression, clinically stable patients with disease progression under immunotherapy should undergo additional short-term follow-up imaging according to the suspected diagnosis. Biopsy should be used cautiously and predominately in curative settings.

Conclusion For response assessment of immunotherapy in clinical studies, the new iRECIST criteria were published in 2017. Outside studies, the application of iRECIST criteria in the clinical routine is subject to several limitations. The recommendations implied in these criteria can, however, be used in conjunction with the current literature as a guideline in clinical practice and outside studies.

Key points:

- Novel immunotherapies can cause atypical response patterns like pseudo-progression
- Compared to real progressive disease, pseudo-progression occurs rather rarely, yet can influence therapy

- Short-term follow-up according to iRECIST can help to distinguish pseudo-progression from real progression
- Hence, radiological follow-up outside clinical studies should be oriented towards iRECIST criteria

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ZUSAMMENFASSUNG

Hintergrund Immuntherapeutika stellen einen wirkungsvollen Therapieansatz für viele vormals schwer therapeutisch zugängliche Tumorentitäten dar. Durch atypische Therapieansprechmuster in Form von Pseudoprogressionen oder Mixed Response sowie ein verändertes Nebenwirkungsspektrum stellen sie die onkologische Bildgebung vor neue Herausforderungen. Dedizierte Kenntnisse hierüber sind für onkologisch tätige Radiologen essenziell, da der radiologische Befund einen wichtigen klinischen Parameter zur Response-Beurteilung darstellt, was wiederum maßgeblich zur Entscheidung über Therapiefortführung und ggf. Kostenübernahme durch die Krankenkassen beiträgt.

Methode Dieses White-Paper basiert auf einem Experten-Meeting in Frankfurt am Main sowie anschließenden Beratungen unter den Autoren und soll auf Grundlage der iRECIST Kriterien eine Orientierung zur in der klinischen Routine praktisch umsetzbaren Response-Beurteilung für onkologische Patienten unter Immuntherapie vermitteln.

Ergebnisse Das radiologische Therapiemonitoring außerhalb von Studien unterliegt inhärenten Limitationen, sollte jedoch nach Meinung des Expertengremiums dennoch in Anlehnung an die iRECIST-Kriterien erfolgen. Hierbei sollte bedacht werden, dass es unter Immuntherapeutika prinzipiell zu Pseudoprogressionen und autoimmunologischen Nebenwirkungen kommen kann. Da die radiologische Bildgebung im Verlauf bis dato die einzige Methode ist, um einen echten Progress von einem Pseudoprogress zu unterscheiden, sollte bei klinisch stabilen Patienten mit einem Progress unter Immuntherapie eine kurzfristige Verlaufskontrolle in Orientierung an der bestehenden Verdachtsdiagnose erfolgen; die Biopsie zur Differenzierung sollte zurückhaltend und vor allem im kurativen Setting genutzt werden.

Schlussfolgerung Für die Response-Beurteilung im Studiensetting wurden 2017 die neuen iRECIST-Kriterien für Immuntherapien publiziert. Außerhalb von Studien ist die Verwendung von iRECIST in der klinischen Routinebefundung nur mit Limitationen möglich. Die in iRECIST implizierten Empfehlungen können jedoch in Zusammenschau mit der aktuellen Literatur als Richtschnur in der klinischen Praxis und außerhalb von Studien dienen.

Introduction

Immunotherapeutics are drugs allowing targeted treatment of tumors using molecular modulation of immunological processes [1]. They have been increasingly used in recent years in personalized cancer treatment so that they now are well established in first- and second-line therapies and in later treatment regimens. Moreover, a number of novel substances are currently in preclinical development and clinical testing (phase 0–III). They allow long-term progression-free or relapse-free disease courses in some tumors that were previously difficult to access with chemotherapy or were refractory, such as metastasized melanoma. The most important tumor entities for which the therapeutic outcome has been able to be improved by the use of immunotherapeutics are malignant melanoma, renal cell carcinoma, Hodgkin lymphoma, lung cancer (particularly, non-small-cell lung cancer (NSCLC)), squamous cell carcinoma of the head/neck region, colon cancer, and urothelial cancer [2–7]. Newer studies were also able to show an advantage of the combined use of conventional chemotherapy and new immunotherapeutics in NSCLC [8–10].

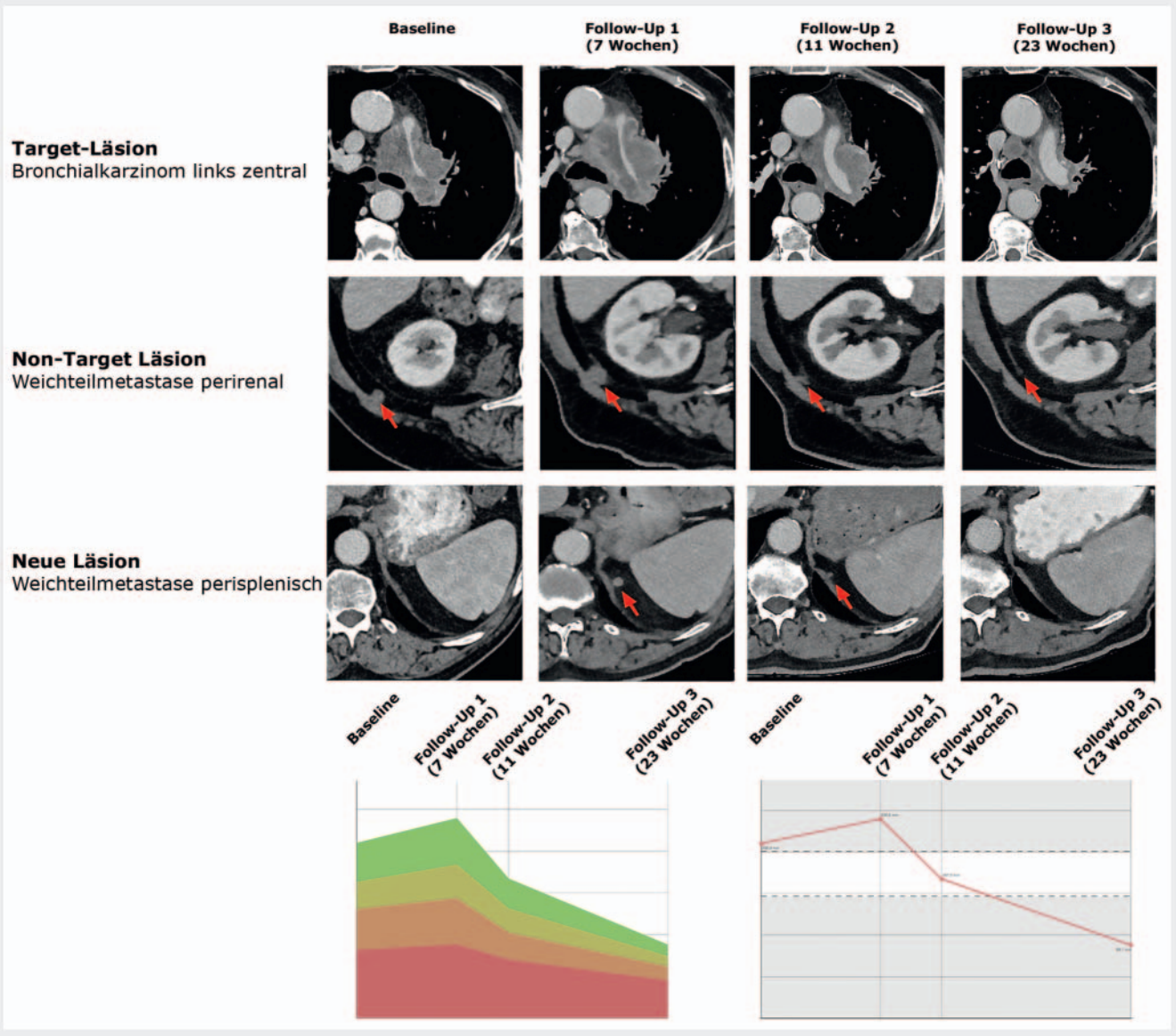
The mechanism of action of the substances currently in clinical use is based on modulation of the T-cell activation that counteracts the immune evasion of tumor cells. The molecular target structures currently primarily in use for this purpose are “cytotoxic T-lymphocyte antigen 4” (CTLA-4), “programmed death 1 receptor” (PD-1), and its ligands “programmed death ligand 1/2” (PD-L1/2) [11, 12]. ▶ **Table 1** provides an overview of the currently approved substances.

At present, high-resolution imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), are the most clinically established biomarkers for response evaluation of immunotherapies. However, there are two pitfalls of immunotherapy that complicate radiological disease monitoring: immunomodulatory therapy can result in atypical response patterns including a divergent treatment response (“mixed response”) as well as a delayed response seen after an initial increase in tumor size (“pseudo-progression”) (▶ **Fig. 1**). This pseudo-progression may be caused by the initial increase in preexisting tumor lesions regarding size and/or number [13]. The invasion of immune cells followed by a change in tumor microenvironment is considered to cause this phenomenon but true tumor progression in the interval between initial imaging and onset of action is another possible explanation. However, rapid tumor progression after the start of treatment without secondary tumor response (“hyperprogression”) has also been described in individual case reports.

According to current literature, the frequency of pseudo-progression seems to be variable and depends on the therapeutic agent, drug combinations and the underlying tumor. However, the currently available data are still limited since clinical studies are primarily focused on the safety and efficacy of the new immunotherapeutics and were evaluated with RECIST 1.1 as the primary outcome parameter and a later treatment response was sometimes not recorded. Therefore, pseudo-progression, if present is

▶ **Table 1** Currently approved immune checkpoint inhibitors with molecular target and clinical application (at date of submission).

drug	target	clinical application
Nivolumab	PD-1	NSCLC, melanoma, squamous cell carcinoma of the head and neck, RCC, urothelial carcinoma, Hodgkin disease
Pembrolizumab	PD-1	NSCLC, melanoma, RCC, urothelial carcinoma, Hodgkin disease
Ipilimumab	CTLA-4	melanoma, RCC
Atezolizumab	PD-L1	NSCLC, urothelial carcinoma
Durvalumab	PD-L1	NSCLC



▶ **Fig. 1** Exemplary case of pseudo-progression in a patient with known non-small cell lung cancer (NSCLC) treated under immunotherapy: In follow-up 1, moderate progression of the primary tumor, size progression of a soft tissue metastasis next to the right kidney and new appearance of a perisplenic soft-tissue metastases can be depicted, leading to an "unconfirmed progressive disease" (iUPD). At the second follow-up, all lesions showed a decrease in size leading to a "stable disease" – the initially diagnosed progression could not be confirmed. According to RECIST 1.1, the progression observed in the first follow-up would have led to the decision to stop therapy.

▶ **Table 2** Pseudo-progression rates according to different studies that investigated immune checkpoint inhibitors.

tumor	study subjects	drug	pseudo-progression rate	study
Melanoma	n = 227	Ipilimumab	9.7 %	Wolchok et al., 2009
	n = 327	Pembrolizumab	7.3 %	Hodi et al., 2015
	n = 107	Nivolumab	10.3 %	Hodi et al., 2014
NSCLC	n = 495	Pembrolizumab	3.2 %	Garon et al., 2015
	n = 56	Nivolumab	0.0 %	Nishino et al., 2016
	n = 292	Nivolumab	5.4 %	Borghaei et al., 2015
RCC	n = 168	Nivolumab	1.8 %	Motzer et al., 2015
Bladder cancer	n = 65	Atezolizumab	1.5 %	Powles et al., 2014
Squamous cell carcinoma	n = 32	Pembrolizumab/Nivolumab	0.0 %	Saâda-Bouzid et al., 2017
	n = 60	Pembrolizumab	1.7 %	Seiwert et al., 2016

not uniformly recorded in many studies. According to a review article by Chiou and Burotto [13], the frequency of pseudo-progression in metastasized malignant melanoma is approximately 10 %. For instance, transient pseudo-progression with subsequent treatment response was described in 9.7 % of cases of malignant melanoma treated with ipilimumab (anti-CTLA-4) in a study by Wolchok et al. [14], while Hodi et al. reported a pseudo-progression rate of 10 % in melanoma patients treated with nivolumab (anti-PD-1) [15]. In another study by Hodi et al. [16], initial pseudo-progression with subsequent significant treatment response was seen in 5 % of patients with advanced malignant melanoma treated with pembrolizumab (anti-PD-1) and delayed slow treatment response was seen in 3 % of cases. Compared to malignant melanoma, the currently available data regarding pseudo-progression under immunotherapy for other tumor entities is sparse and is based partially on case reports: Tanizaki et al. [17] reported pseudo-progression in two patients with non-small-cell lung cancer (NSCLC) under treatment with nivolumab with complete response of liver metastases, as subsequently confirmed by histopathology. In contrast, in a NSCLC study, Nishino et al. [18] recently did not observe any pseudo-progression under nivolumab treatment (0 of 56 patients). A larger study regarding the treatment of NSCLC with pembrolizumab showed pseudo-progression in 16/495 patients (3.2 %) [5]. Other study data describes a rate of pseudo-progression of 1.8 % (3 of 168 patients) in renal cell carcinoma (RCC) [19] and of 1.5 % (1 of 65 patients) in bladder cancer [20]. Based on the available data, it can be assumed that pseudo-progression typically occurs within the first three months after start of immunotherapy, while later progression (> 6 months after the start of treatment) is more likely related to an real tumor progression. However, systematic studies regarding the time of occurrence of pseudo-progression as a function of tumor entity and treatment regimen are currently lacking. An overview of the pseudo-progression rates according to disease and treatment regimen is provided in ▶ **Table 2**.

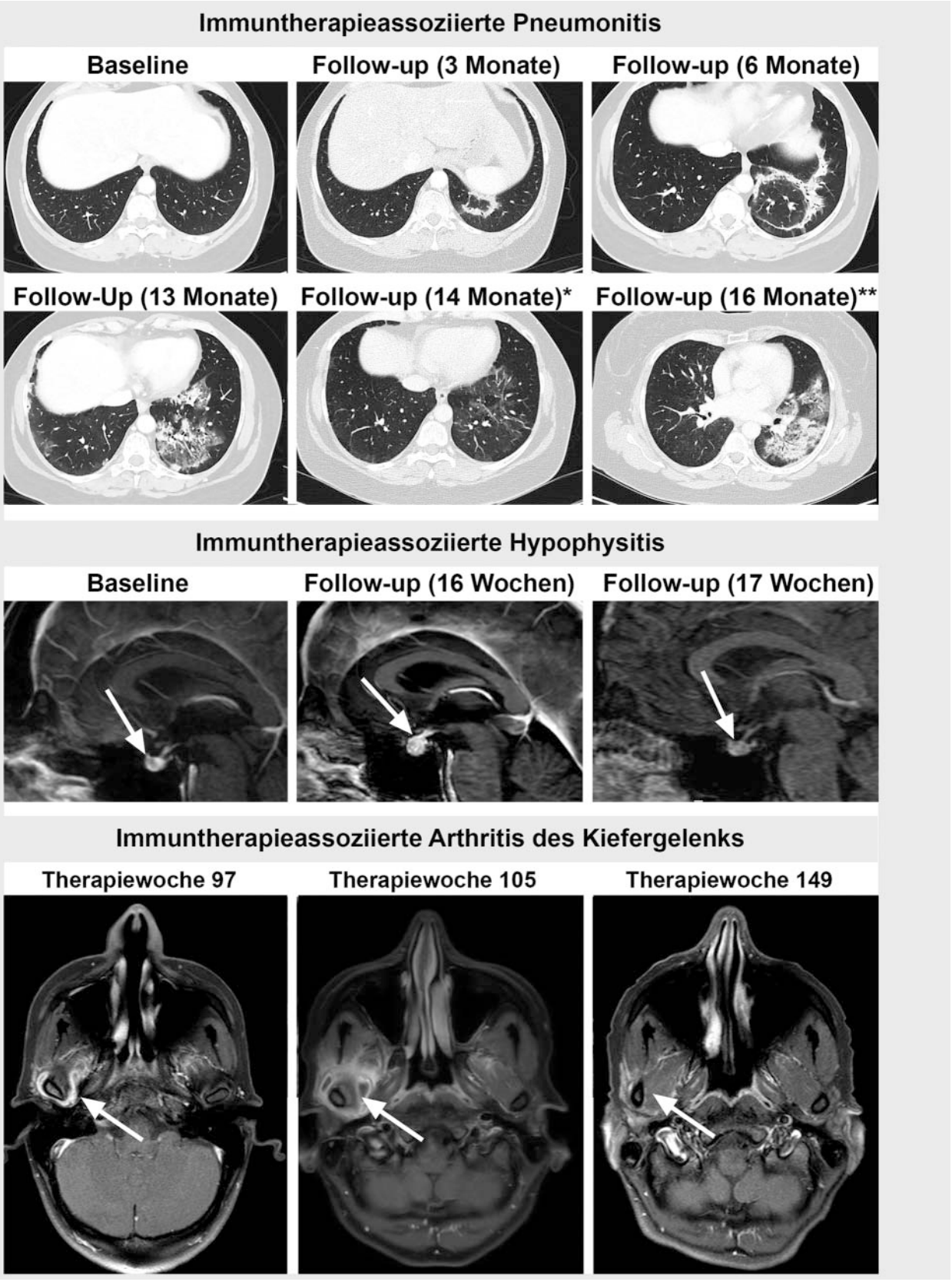
Apart from pseudo-progression and positive treatment effects, immunotherapy may also result in autoimmune side effects, such as immune therapy-associated pneumonitis, reactive lymphadenopathy, sarcoidosis-like reactions, colitis, or hypophysitis. These can limit therapy depending on their extent and must be detected properly and not be mistaken for tumor progression (▶ **Fig. 2**, ▶ **Table 3**). Therefore we refer to detailed review articles [21, 22] for information regarding the various patterns of manifestations in the different organs.

iRECIST

Radiological criteria for response monitoring were developed in clinical studies under defined treatment conditions. The transferability to the clinical radiology routine is limited due to various factors like necessary pauses of therapy, dose modifications, individual treatment concepts, or a lack of clinical information or prior imaging. However, treatment monitoring under immunotherapy should be as accurate as possible in the clinical routine and be performed under consideration of possible atypical response patterns or autoimmune side effects. An adapted application of the established RECIST 1.1 or iRECIST criteria can be helpful in the clinical routine and allow a more objective assessment of treatment response. However, this is sometimes already required by health insurances when an individual cancer treatment is requested.

The atypical response patterns under immunotherapy are sometimes incorrectly interpreted as tumor progression based on classical response criteria (like RECIST 1.1) resulting in an unjustified discontinuation of treatment. Therefore, the immune-related response criteria (irRC) were developed in 2009 on the basis of the WHO criteria and were adapted in 2013 to RECIST 1.0 and in 2014 to RECIST 1.1 [6–8]. In 2017, the iRECIST criteria that represent a further development of the RECIST 1.1 criteria with respect to atypical response patterns under immunotherapies were published by the official RECIST working group [23].

The primary imaging modalities used are contrast-enhanced CT and MRI with with an axial slice thickness of ≤ 5 mm being preferred for best possible reproducibility. For details regarding the definition of target and non-target lesions, please refer to the corresponding literature [23, 24]. In the case of iRECIST, the definition of target and non-target lesions in the initial examination



▶ **Fig. 2** Immunotherapy-associated side effects: pneumonitis, hypophysitis and arthritis of the mandibular. joint. * = after corticosteroid therapy * * = after stop of corticosteroid therapy.

▶ **Table 3** Incidence and occurrence of pneumonitis and colitis, two important adverse reactions to immunotherapy.

adverse reaction	drug	rate of adverse reactions	median time to occurrence
Pneumonitis	Nivolumab/Pembrolizumab	2.7 % [20]; 3.6 % [21]	4–6 [20]
	Atezolizumab	1.3 %[21]	4–6 [20]
	Ipilimumab	0.4 % [22]	1–3 [22]
	Combination therapy PD1/PD-L1 + Ipilimumab	10 % [20]	2–8 [20]
Colitis	Nivolumab/Pembrolizumab	1–2 % [23, 24]	3 [25, 26]
	Ipilimumab	8–22 % [27]	1–6 [26]

(baseline) is performed analogously to RECIST 1.1. Target lesions (TL) are defined as solid tumor manifestations that can be reproducibly measured with a minimum size in the long axis diameter (LAD) of ≥ 10 mm and lymph node metastases with a short axis diameter (SAD) of ≥ 15 mm. Of the potential targets, up to 5 lesions per patient and 2 lesions per organ can be defined as target lesions. Non-target lesions (non-TLs) are defined as lesions with an insufficient measurement and are qualitatively recorded without an absolute measurement (▶ **Fig. 3**).

The occurrence of new lesions is handled differently in iRECIST compared to RECIST 1.1. In the case of RECIST 1.1, new tumor lesions direcly result in the diagnosis of progressive disease (PD). In contrast, iRECIST differentiates between new measurable and non-measurable lesions. Although new tumor lesions indicate tumor progression analogous to RECIST 1.1 in iRECIST, in the case of a clinically stable disease, this initially unconfirmed tumor progression (iUPD = "unconfirmed progressive disease") must be confirmed (iCPD = "confirmed progressive disease") by a short-term follow-up within 4–8 weeks instead of after 6–12 weeks.

New not definitively tumorous lesions, such as inflammatory lymph nodes, should initially be classified as findings so that treatment can be continued. However, if these lesions are confirmed in the next follow-up examination as tumor lesions, the onset of progressive disease (PD) is retrospectively backdated to the examination that detected the initial occurrence of these lesions.

Treatment response

Treatment response is defined by a combination of the change in target lesions (TLs) and non-target lesions (non-TLs) and the detection of new measurable and/or non-measurable tumor lesions is categorized as:

1. Complete response (iCR): Complete disappearance of all target lesions (TLs) and non-target lesions (non-TLs) or a reduction in the size of pathologically enlarged lymph nodes to a normal short axis diameter (SAD) of less than 10 mm
2. Partial response (iPR): Reduction of the tumor load of the target lesions by at least ≤ 30 % compared to the baseline examination or complete remission of the target lesions but with continued detectability of one or more non-target lesions
3. Stable disease (iSD): the criteria for neither iCR nor iPR are fulfilled

According to iRECIST, in the case of an increasing tumor load in follow-up imaging with clinically stable tumor disease, the following should be initially determined in order to differentiate true tumor progression from pseudo-progression with a course of disease that is potentially advantageous for the patient:

1. Unconfirmed progressive disease (iUPD) caused by an increase in the sum of all TLs by at least ≥ 20 % (at least ≥ 5 mm) compared to the lowest TL sum in the course (so-called nadir; with lack of tumor reduction identical with the baseline), definitive progression of the non-TLs ("unequivocal progression") or the occurrence of new measurable and/or non-measurable tumor lesions.

Unconfirmed tumor progression should be reevaluated in the case of clinically possible pseudo-progression in the next follow-up examination within a shorter interval of 4–8 weeks to differentiate this pseudo-progression from "true" progression.

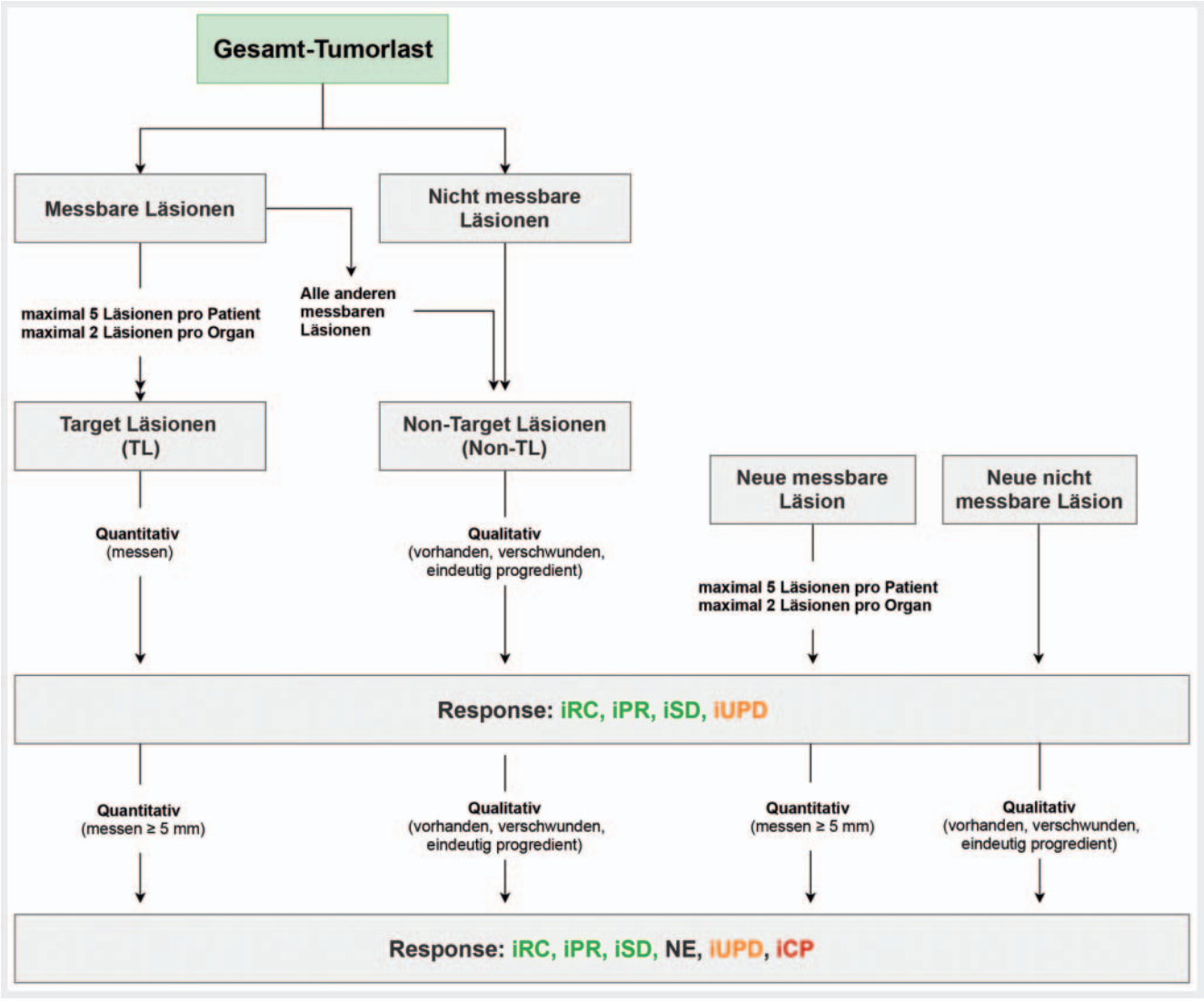
1. Confirmed progressive disease (iCPD) is confirmed when the target lesion sum continues to increase (at least ≥ 5 mm) and/or the non-target lesions are progressive and/or the new measurable or non-measurable lesions in the previous examination increase in size and/or number.

If the tumor progression is not confirmed in the subsequent follow-up, the patient remains in the stage of unconfirmed tumor progression (iUPD) until further progression is seen (iCPD), if there is a reduction to the baseline level (iSD), if there is a reduction of over 30 % compared to baseline (iPR) or complete remission (iCR) is achieved. If there is no confirmation of the first iUPD after 4–8 weeks subsequent further follow-up examinations should then be performed within the regular intervals, e. g., after 8, 16, and 24 weeks.

Response evaluation under immunotherapy: Recommendations and orientation for clinical practice

Oncological imaging outside study protocols

Based on RECIST 1.1 and iRECIST, high-resolution CT is the standard for staging of the chest and abdomen, while MRI is used for imaging of the neurocranium or the extremities. With regards to



▶ **Fig. 3** Schematic overview of response evaluation according to iRECIST.

choosing the optimal imaging modality, examination protocol and interval, current AWMF guidelines for the corresponding tumor entity can provide orientation. Since modern MRI units increasingly improve the intermodal comparability between MRI and CT, a switch from CT to MRI can be considered for follow-up, particularly in the case of long recurrence-free courses. The following time points based on iRECIST can be used as imaging intervals under immunotherapy (also see the expert opinion below): at any time in the case of clinical worsening, otherwise:

- regular follow-up interval after 8–12 weeks in iSD, iPR, and iCR
- shorter follow-up interval of 4–8 weeks in iUPD

It must be taken into consideration that "day 0" of the initial imaging often does not correspond to the treatment start day. In this regard it is recommended that the imaging that serves as the baseline examination is as close as possible to treatment initiation and should at least not be older than 4 weeks, because otherwise any changes in tumor size and/or new tumor lesions not shown in the baseline examination occurring by the start of treatment can result in a misinterpretation in the first follow-up.

A shorter interval of 4–8 weeks after detection of an iUPD seems reasonable in the case of possible pseudo-progression over the course of the disease, in clinically stable patients or in the case of lack of other treatment options. According to the expert opinion, the concrete time should be based on the patient's condition and the suspected diagnosis: after 4 weeks in the case of suspected true progression, after 6–8 weeks in the case of suspected pseudo-progression so that a possible later response is not missed. In the case of clinical worsening, imaging should be performed again immediately.

Response evaluation over the course of the disease

In principle the use of iRECIST in routine reporting under immunotherapies is considered as helpful. However, a direct translation to the clinical setting is often not possible as a result of numerous limitations. Among others, a lack of clinical information (e. g. re-

garding the start of treatment or treatment breaks), personalized treatment concepts (like combination of different anti-cancer substances), parallel effects (like the abscopal effect in parallel radiation therapy at another location), and missing or insufficient prior imaging are an inherent problem of long-term treatment monitoring for radiologists. As a result, for example, a patient without diagnostic imaging at the time of the best treatment response with the lowest tumor burden (so called nadir) compared to previous imaging could be incorrectly evaluated as stable disease (SD) although the missing imaging would actually show a relevant increase in the tumor burden in terms of progressive disease (iUPD).

According to expert opinion, treatment monitoring under immunotherapy should be performed when possible in the clinical routine ideally based on the iRECIST criteria in relation to the definition and number of target lesions and non-target lesions and the method for new lesions. In the clinical routine this would concretely mean a measurement of the 5 maximum target lesions and naming of the additional TLs and non-TLs, combined into groups if applicable, seems to be adequate. Although this information is currently already included in most reports, but it is often provided in a minimally structured and not always RECIST-compliant manner (e. g. measurement of lesions < 10 mm with consecutively high measurement variance, measurement of different, sometimes divergent or more than 5 lesions). This problem could be minimized by structured listing of the TLs and non-TLs. This could save time and simplify re-measurement of predefined lesions and recording of the current measurements during follow-up examinations compared to an approach in which divergent and sometimes more than 5 lesions are selected, remeasured and listed with serial number and table position in prose form. Special oncological software solutions that allow a simplified, more time-efficient, and iRECIST-compliant response evaluation seem advantageous here. Alternatively, semiautomatic analyses of response on a "time-point" basis can already be performed online with the help of cost-free RECIST calculators (like from the German Radiological Society (DRG)) under www.befundung.drg.de/de). However, experts are aware that the use of oncological software solutions for optimized reporting of findings currently still has numerous limitations such as sometimes impossible or only suboptimal IT integration in existing radiology reporting systems and that the high purchasing costs are not taken into consideration in reimbursement by health insurance. Therefore, this cannot be required as a standard for routine reporting.

A further basic problem is that the majority of cancer patients are undergoing non-standardized treatment regimes in contrast to clear defined study settings and complete transfer of all necessary clinical information cannot always be ensured. As a consequence, treatment monitoring with long-term evaluation analogous to iRECIST criteria is sometimes not consistent and possible for every tumor patient. However, at least the structured determination and documentation of the total tumor burden at the particular scan time and an evaluation in comparison to the most recent prior examination based on iRECIST seems possible without relevant additional work. In this procedure the referring physician would receive a structured evaluation for every time point (in comparison to the most recent prior examination) but would also have the option to analyze and evaluate the long-term course on the basis of the total tumor burden (including nadir) previously acquired and documented in the same way.

Finding terminology: Use caution regarding key words from the study setting

When reporting the findings from oncological examinations of patients undergoing immunotherapy, it should be taken into consideration that the terms "progressive disease", "partial response", and "stable disease" are clearly defined within the established criteria and noncritical use can give a false impression in interdisciplinary communication. To avoid misunderstandings between oncological clinical disciplines and radiologists possibly resulting in unjustified treatment changes, the authors suggest that these terms should be avoided in the radiology report outside of studies. Instead, terminology should be oriented towards existing criteria (in immunotherapy according to iRECIST and in conventional chemotherapy according to RECIST 1.1) such as:

- Compared to month/year, "stable tumor status" or "stable finding", instead of iSD.
- Compared to month/year, "very good treatment response" or a "significant reduction in tumor size", instead of iPR.
- Compared to month/year, a "significant increase in tumor size" or "progressive tumor lesions with respect to number and/or size" seen for the first time; optionally in the case of suspicion of pseudo-progression on imaging, compared to month/year, "significant increase in tumor size possibly related to/or caused by pseudo-progression", instead of iUPD.
- Compared to month/year, "further increase in tumor size" or "further progression of tumor lesions with respect to number and/or size suspicious for real tumor progression", instead of iCPD.

Uniform language should be discussed and used with the referring colleague depending on the local preference.

Disease progression versus pseudo-progression

RECIST 1.1 and iRECIST are designed for use under defined clinical study conditions. However, due to the increased use of immune-modulating treatments also in daily radiology practice, it is necessary to be familiar with the possibility of an atypical response when reporting subsequent examinations. The concept of "unconfirmed progression (iUPD)", which was added to iRECIST to account for the possibility of pseudo-progression under immunotherapy, can be used for orientation purposes in these cases.

The following aspects should be taken into consideration in the evaluation of a possible pseudo-progression:

1. In principle, pseudo-progression can occur under treatment with all currently approved immunotherapeutics. This can be expressed as size progression of existing lesions as well as new lesions compared to the baseline examination [25]. To date, there is no noninvasive biomarker (laboratory tests, morphology, metabolic) that allows a reliable, routine ad hoc differentiation of pseudo-progression from true tumor progression under immunotherapy. Radiological follow-up might be helpful for differentiation and confirmation of the suspected diagnosis.

2. It total, the probability of pseudo-progression is to be considered markedly lower compared to the presence of true tumor progression: up to 10 % in malignant melanoma, up to 2 % in squamous cell carcinoma of the head-neck region, between 3 % and 5 % in the case of NSCLC, between 1 % and 4 % in the case of renal cell carcinoma [6, 15, 16, 19, 26–28]. Since the response rates for immunotherapy are between 20 % and 40 % depending on the primary disease, the probability of pseudo-progression must be considered significantly lower than that of true disease progression. However, for the individual tumor patient, the occurrence of an initially less probable pseudo-progression can be of significant advantage for life in the long term [26, 29, 30].
3. The extent of the progression is not a valid predictor of whether the progression is pseudo-progression or true progression. Particularly in the case of malignant melanoma and NSCLC, in the case of pronounced tumor increase pseudo-progression with a favorable long-term course or a fulminant tumor progression ("hyperprogression") could be present [31–33]. Increases in size of up to 163 % with consecutive size regression have been described in individual cases in the context of subsequently confirmed pseudo-progression [34].
4. Typically pseudo-progression occurs at the start of therapy, i. e., in the first 6 months or in the first two follow-up examinations after the start of treatment according to the expert panel. Late progression seen several months after the start of therapy or after a treatment response is probably "true" disease progression.
5. Currently available equipment technology allows visualization of small lesions, even very small, previously occult lesions in some follow-up examinations. It should be taken into consideration that not every newly detected lesion is suspicious for disease progression and an inflammatory genesis or autoimmune side effect of tumor therapy could be the real cause (finding or treatment side effect). Progression should be determined based on the described RECIST 1.1 or iRECIST criteria that were defined under consideration of biological and equipment-based measurement variances.
6. In the case of initial lesion progression, the clinical evaluation of the patient should play a central role when making decisions regarding the continuation of treatment. The iRECIST guidelines clearly recommend careful consideration of continuation of immunotherapy at the initial occurrence of tumor progression (iUPD) and discussion with the patient only in a subjectively stable clinical situation.
7. The indication for biopsy for differentiation of pseudo-progression from true progression should be determined based on iRECIST particularly in the curative setting in order to allow early treatment adjustment in the case of true progression. However, it must also be stated that it can sometimes be very difficult or impossible for the pathologist to provide reliable differentiation based on tissue samples.

In summary, modern immunotherapies play an important role in personalized cancer treatment. In oncological imaging, atypical treatment response patterns and an altered spectrum of adverse reactions to immunotherapeutics sometimes present a challenge. However, the iRECIST recommendations can be helpful in this case and serve as a guide in clinical practice and outside studies.

Conflicts of interest

All authors received expense allowance and travel cost compensation by Bristol-Myers Squibb for attending the expert meeting in Frankfurt am Main.
Wieland Sommer is the founder of Smart Reporting GmbH, a software for structured reporting.

References

[1] Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nature reviews. Cancer 2012; 12: 252–264

[2] Seetharamu N, Preeshagul IR, Sullivan KM. New PD-L1 inhibitors in non-small cell lung cancer – impact of atezolizumab. Lung Cancer (Auckland, N.Z.) 2017; 8: 67–78

[3] Wolchok JD, Chiarion-Sileni V, Gonzalez R et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. The New England journal of medicine 2017; 377: 1345–1356

[4] Hude I, Sasse S, Engert A et al. The emerging role of immune checkpoint inhibition in malignant lymphoma. Haematologica 2017; 102: 30–42

[5] Garon EB, Rizvi NA, Hui R et al. Pembrolizumab for the treatment of non-small-cell lung cancer. The New England journal of medicine 2015; 372: 2018–2028

[6] Ferris RL, Blumenschein G, Fayette J et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. The New England journal of medicine 2016; 375: 1856–1867

[7] Sharma P, Retz M, Siefker-Radtke A et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): A multicentre, single-arm, phase 2 trial. The Lancet Oncology 2017; 18: 312–322

[8] Frederickson AM, Arndorfer S, Zhang I et al. Pembrolizumab plus chemotherapy for first-line treatment of metastatic nonsquamous non-small-cell lung cancer: A network meta-analysis. Immunotherapy 2019; 11: 407–428

[9] Gandhi L, Rodríguez-Abreu D, Gadgeel S et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. The New England journal of medicine 2018; 378: 2078–2092

[10] Langer CJ, Gadgeel SM, Borghaei H et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The Lancet Oncology 2016; 17: 1497–1508

[11] Callahan MK, Postow MA, Wolchok JD. Targeting T Cell Co-receptors for Cancer Therapy. Immunity 2016; 44: 1069–1078

[12] Shih K, Arkenau HT, Infante JR. Clinical impact of checkpoint inhibitors as novel cancer therapies. Drugs 2014; 74: 1993–2013

[13] Chiou VL, Burotto M. Pseudoprogression and Immune-Related Response in Solid Tumors. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2015; 33: 3541–3543

[14] Wolchok JD, Hoos A, O'Day S et al. Guidelines for the evaluation of immune therapy activity in solid tumors: Immune-related response criteria. Clinical cancer research: an official journal of the American Association for Cancer Research 2009; 15: 7412–7420

[15] Hodi FS, Sznol M, Kluger HM et al. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2014; 9002: 9002

[16] 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. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2016; 34: 1510–1517

[17] Tanizaki J, Hayashi H, Kimura M et al. Report of two cases of pseudoprogression in patients with non-small cell lung cancer treated with nivolumab-including histological analysis of one case after tumor regression. Lung cancer (Amsterdam, Netherlands) 2016; 102: 44–48

[18] Nishino M, Ramaiya NH, Chambers ES et al. Immune-related response assessment during PD-1 inhibitor therapy in advanced non-small-cell lung cancer patients. Journal for immunotherapy of cancer 2016; 4: 84

[19] Motzer RJ, Rini BI, McDermott DF et al. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2015; 33: 1430–1437

[20] Powles T, Eder JP, Fine GD et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014; 515: 558–562

[21] Nishino M, Giobbie-Hurder A, Hatabu H et al. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. JAMA oncology 2016; 2: 1607–1616

[22] Gedye C, van der Westhuizen A, John T. Checkpoint immunotherapy for cancer: Superior survival, unaccustomed toxicities. Internal medicine journal 2015; 45: 696–701

[23] Seymour L, Bogaerts J, Perrone A et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology 2017; 18: e143–e152

[24] Ferté C, Marabelle A. iRECIST: A clarification of tumour response assessment in the immunotherapy era. European journal of cancer (Oxford, England: 1990) 2017; 77: 165–167

[25] Wang Q, Gao J, Wu X. Pseudoprogression and hyperprogression after checkpoint blockade. International immunopharmacology 2018; 58: 125–135

[26] Borghaei H, Paz-Ares L, Horn L et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. The New England journal of medicine 2015; 373: 1627–1639

[27] Kumagai T, Kimura M, Inoue T et al. Delayed pseudoprogression of lung adenocarcinoma accompanied with interstitial lung disease during chemotherapy after nivolumab treatment. Thoracic cancer 2017; 8: 275–277

[28] Seiwert TY, Burtness B, Mehra R et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): An open-label, multicentre, phase 1b trial. The Lancet Oncology 2016; 17: 956–965

[29] Robert C, Long GV, Brady B et al. Nivolumab in previously untreated melanoma without BRAF mutation. The New England journal of medicine 2015; 372: 320–330

[30] Herbst RS, Baas P, Kim DW et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. The Lancet 2016; 387: 1540–1550

[31] 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. Clinical cancer research: an official journal of the American Association for Cancer Research 2017; 23: 1920–1928

[32] Kato S, Goodman A, Walavalkar V et al. Hyperprogressors after Immunotherapy: Analysis of Genomic Alterations Associated with Accelerated Growth Rate. Clinical cancer research: an official journal of the American Association for Cancer Research 2017; 23: 4242–4250

[33] Saâda-Bouzid E, Defaucheux C, Karabajakian A et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Annals of oncology: official journal of the European Society for Medical Oncology 2017; 28: 1605–1611

[34] Chae YK, Wang S, Nimeiri H et al. Pseudoprogression in microsatellite instability-high colorectal cancer during treatment with combination T cell mediated immunotherapy: A case report and literature review. Oncotarget 2017; 8: 57889–57897