Personalized chemotherapy of lung cancer: What the radiologist should know

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Abstract  Lung cancer is the leading cause of deaths due to cancer in France. More than half of lung cancers are discovered at an advanced-stage. New anticancer treatment strategies (i.e., the so-called personalized or targeted therapy) have recently been introduced and validated for non-small-cell lung cancer (NSCLC), in addition to or in association with standard chemotherapy. Personalized therapy includes tyrosine kinase inhibitors (TKIs), antiangiogenic treatments and immunotherapy. Because these treatments may be responsible for atypical thoracic adverse effects and responses as compared to standard chemotherapy, RECIST 1.1 criteria may be inadequate to evaluate the responses to these agents. The goal of this article was to review personalized treatment strategies for NSCLC, to consider the therapy-specific responses and thoracic complications induced by these new therapeutic agents and finally to discuss future directions for the personalized assessment of tumor response.

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Lung cancer is the leading cause of cancer deaths worldwide [1]. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers and is detected at a late stage in approximately 65% of patients when removal of the tumor by surgery is no longer feasible [2]. The 5-year survival rate of such patients with metastatic lung cancer is lower than 5%, whatever the stage [3].

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Recently introduced treatment options for NSCLC, in addition or in association with standard chemotherapy, are based on a more precise characterization of the lung cancer tissue, both in respect to its histological subtype (squamous-cell carcinoma versus adenocarcinoma) and genotype, via the use of molecular tumor markers and the detection of oncogenic abnormalities [4]. The implementation of “personalized” treatments that target tumors of a given biological and genetic profile are therefore subject to prior characterization by pathological and molecular genetics methods [5]. The most compelling example is the treatment of lung adenocarcinomas harboring epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations with tyrosine kinase inhibitors (TKI). The role of angiogenesis inhibitors and immunotherapy in NSCLC management is also growing. The increased efficiency, measured in terms of progression-free survival and/or overall survival, is encouraging. However, these new treatment strategies may result in responses that are very different from those observed with standard cytotoxic chemotherapy on imaging. Consequently, it has been suggested that the classical RECIST 1.1 criteria [6] used to assess the efficacy of a therapy should be revised.

Radiologists are involved in several stages of the management of patients with suspected or confirmed lung cancer, both before [7] and during treatment. They must be able to adapt to new constraints arising from changes in therapeutic approaches [8]. When the diagnosis is based on the results of histopathological analysis of percutaneous, transthoracic biopsy, the samples collected must comply with the quality requirements needed to meet the new expectations of oncologists in terms of molecular biology and histology [9]. RECIST 1.1 criteria are being increasingly used in the context of post-therapeutic follow-up and interdisciplinary team meetings [10], and should take into account the changes arising from personalized treatment.

The aim of this paper was to review the new targeted therapies for lung cancer and their radiographic responses, including thoracic adverse effects, which radiologists need to be familiar with to correctly interpret computed tomography (CT) images during post-therapeutic follow-up. Finally, we will discuss changes to the assessment criteria used for these new treatment options.

Overview

Polymorphism of lung tumors

The numerous histological subtypes identified for lung cancer reflect variations of the tumor genome ranging from point mutations or the loss or gain of several nucleotides to the deletion or amplification of large chromosomal regions, or even whole chromosomes. Oncogenes are generally enabled by “activating” mutations or translocations, or in some cases gene amplification, whereas tumor suppressor genes are silenced by “inactivating” mutations, deletions or gene promoter methylation.

Diagnosing molecular abnormalities

In France, the Institut National du Cancer (INCa) has implemented one of the most advanced cancer molecular diagnosis services based on 28 molecular genetics platforms throughout France that diagnose the molecular and genetic abnormalities that can be targeted by specific therapies. This diagnostic service is free and available to all patients treated in France. The Biomarkers France study enables 6 molecular abnormalities to be diagnosed in nearly 20,000 patients with advanced-stage NSCLC per year: EGFR, KRAS, HER2 and BRAF mutations and ALK and ROS1 gene rearrangements (Fig. 1) [11].

The concept of targeted therapy

The use of a targeted therapy is subject to the tumor having a given molecular mutation; therefore, the patients eligible for each specific treatment represent only a subset of all patients [12]. The concept of targeted therapy can, by extension, be broadened to include all molecules that inhibit tumor growth, such as angiogenesis inhibitors and immunotherapy, even though no predictive markers of the response to angiogenesis inhibitors or immune checkpoint inhibitors have been reported to date.

In practice, two therapeutic classes are currently available and readily identifiable: TKIs (identified by the suffix “-nib” on their INN, e.g. gefitinib, erlotinib, afatinib, crizotinib, etc.), and monoclonal antibodies targeting transmembrane proteins (identified by the suffix “-mab” on their INN, e.g. cetuximab, bevacizumab, necitumumab or nimolumab) (Table 1) [13].

Tyrosine kinase inhibitors (TKIs)

Mutation of the EGFR gene

EGFR mutations are known to “drive” certain lung cancers, especially in nonsmokers. The ATP binding pocket of the intracytoplasmic domain of the EGFR receptor exhibits a tyrosine kinase type activity and such mutations result in continuous receptor activation. This in turn activates the proteins of the intracellular signaling pathways involved in tumor cell proliferation, resistance to apoptosis, and cell migration. In patients harboring activating EGFR mutations, tumor cells and all the steps leading to tumorigenesis are literally dependent on the activation of this kinase. The most frequently observed mutations are L858R on exon 21 and the deletion of exon 19. EGFR mutations are observed

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Figure 1. Pie chart showing the genomic subtypes of lung adenocarcinomas based on different driver mutations detected by testing 9911 patients included in the Biomarqueur France cohort (modified from ref. [10]).
more frequently in adenocarcinoma, women, nonsmokers (33.2% of nonsmokers versus 4.2% of smokers) and patients of Asian origin. EGFR mutations are found in 10–16.6% of Caucasian patients with adenocarcinoma, versus 30–50% in Asian patients [14].

First-generation EGFR TKIs include gefitinib, erlotinib and afatinib. They improve progression-free survival [15] when compared with standard chemotherapy in randomized studies, and in certain cases the overall survival [16]. Initially, their efficacy is often spectacular, but only to be overcome by the appearance of resistance after about a year, which inevitably leads to disease progression. Of the various mechanisms of resistance, the mutation T790M of the EGFR is the most common (50%). Finally and quite surprisingly, histological changes are sometimes observed, with transformation of NSCLC into small-cell carcinoma at cells and epithelial-mesenchymal transition [17]. Finding the mechanism of resistance is recommended of the use of third-generation TKIs is subject to the presence of the T790M mutation [18]. It is also advised to perform a new biopsy, however this is not always possible especially if the site of recurrent NSCLC is the brain or bone [19]. Alternative methods based on detecting molecular abnormalities in circulating tumor DNA are currently under development.

**TKI toxicity**

Most commonly, TKI toxicity affects the skin, digestive tract and more rarely the lungs. Interstitial lung disease (ILD) occurs in approximately 1% of subjects treated with first-generation TKIs [20]. It is observed more frequently in Japanese patients, with frequencies ranging from 2.4% to 5.5% [19]. Beom et al. reported ILD in 15/1114 (1.3%) patients with NSCLC treated with erlotinib in Korea and ILD resulted in death in 9 of them (60%) [21]. ILD has been reported in to result in death in 20–68% of Asian patients. Clinically, the patients present with continuous dyspnea and coughing, and 80% of cases occur within the first 8 weeks following the initiation of treatment [21]. CT shows infiltrates as ground glass opacities or multiple consolidations [22]. Endo et al. described four patterns of CT findings [22]: a nonspecific localized ground glass attenuation; multifocal airspace consolidations; ground glass attenuation with random interlobar septal thickening; extensive ground glass attenuations or airspace consolidations. The most frequently observed pattern was localized ground glass attenuation; the most serious was extensive ground glass attenuations or airspace consolidations.

Bilateral pneumothorax secondary to a significant loss of tumor tissue has been reported in the 4 weeks following the initiation of gefitinib [23] or erlotinib (Fig. 2) [24].

**Revised RECIST criteria**

RECIST 1.1 criteria were updated from RECIST 1.0 criteria and validated to take into account patients treated with TKIs (Boxed text 1) [25]. The response of adenocarcinoma patients with activating mutations to TKI treatment is often important [26] with the size of the target and non-target lesions reducing in a spectacular manner. However, the

<table>
<thead>
<tr>
<th>INN</th>
<th>Brand name</th>
<th>Mode of action</th>
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<tbody>
<tr>
<td>Gefitinib</td>
<td>Iressa®</td>
<td>First-generation EGFR TKI</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Tarceva®</td>
<td>First-generation EGFR TKI</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Giotrif®</td>
<td>Second-generation EGFR TKI</td>
</tr>
<tr>
<td>Rocelitinib</td>
<td></td>
<td>Third-generation EGFR TKI and T790M TKI</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Xalkori®</td>
<td>ALK, ROS and MET protein TKI</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Zykadia®</td>
<td>Second-generation ALK and ROS TKI</td>
</tr>
<tr>
<td>Alectinib</td>
<td>Avastin®</td>
<td>Antiangiogenic drug</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Yervoy®</td>
<td>Immunomodulatory drug CTLA4 checkpoint inhibitor</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td></td>
<td>Anti-PD1 antibody</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Atezolizumab</td>
<td>Anti-PD-L1 antibody</td>
</tr>
</tbody>
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INN: international nonproprietary names; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; TKI: tyrosine kinase inhibitors; anti-PD1: anti-programmed cell death-1; anti-PD-L1: anti-programmed cell death ligand-1; VEGF: vascular endothelial growth factor.

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**Figure 2.** Computed tomography (CT) images in the transverse plane (section thickness, 3 mm) of a 42-year-old woman with stage IV adenocarcinoma harboring an epidermal growth factor receptor mutation treated with a tyrosine kinase inhibitor. a: baseline chest CT image shows multiple bilateral confluent nodules in both lungs; b: chest CT scan after 6 weeks of tyrosine kinase inhibitors treatment demonstrates a marked decrease in lung nodules and occurrence of significant left pneumothorax and limited right pneumothorax; c: follow-up CT scan of the chest after 10 weeks of treatment shows resolution of pneumothorax after drainage of the left pneumothorax and a marked decrease in lung nodules.
Boxed text 1: RECIST 1.1 criteria.
Assessment of target lesions
- **CR:** complete response
  - Complete disappearance of all lesions
  - Short axis of target lymph nodes < 10 mm
- **PR:** partial response
  - $\geq 30\%$ decrease in the sum of larger diameters of target lesions compared with baseline
- **PD:** progressive disease
  - $\geq 20\%$ increase in the sum of larger diameters of target lesions compared with nadir (the smallest sum of larger diameters) AND $> 5$ mm (significance level)
  - Appearance of a new lesion
- **SD:** stable disease
  - $-30\% < \text{size} < +20\%$, compared with nadir
  - Assessment of non-target lesions
- **CR:** complete response
  - Complete disappearance of all non-nodal non-target lesions and all non-target nodes $< 10$ mm (short axis)
  - Return to normal of tumor marker levels, if applicable
- **Non-CR/non-PD:**
  - Persistence of one or more non-target lesions or tumor marker levels $> \text{normal limits}$
- **PD:** progressive disease
  - Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Discontinuation of treatment is therefore contraindicated unless alternative therapy is to be implemented.

The appearance of osteoblastic reactions in patients treated with first-generation TKIs should not be considered as disease progression. Several authors have associated the appearance of such osteoblastic reactions with a favorable outcome for known or occult bone metastases (Fig. 3) [32].

**Anaplastic lymphoma kinase (ALK) gene rearrangement**

The ALK gene encoding the ALK protein kinase is located on the short arm of chromosome 2. In 3–5% of NSCLC cases, especially adenocarcinomas, ALK fuses with another gene, generally **EML4**, which is also located on the short arm of chromosome 2. The fusion or translocation of these two genes results in the continuous activation of the protein kinase ALK, which, likewise to EGFR, activates in turn intracytoplasmic signaling pathway that promotes tumor proliferation. As with EGFR, tumor cells are “addicted” to the activation of this kinase. This rearrangement is most often found in younger, nonsmoking patients (60%) and those for whom the disease was discovered at a late stage with often-serosal involvement [33].

Crizotinib is a tyrosine kinase inhibitor that targets the ALK fusion protein, but also the ROS fusion protein and MET. It has recently marketing authorization for second-line treatment due to its efficacy in patients with ALK gene

**Figure 3.** The flare phenomenon. a: baseline sagittal reconstruction computed tomography (CT) of the spine in a patient with stage IV lung cancer harboring an epidermal growth factor receptor mutation. A few osteoblastic lesions are visible as small round images of high density within vertebral bodies and the sternum (arrow); b: sagittal reconstruction CT of the spine at the same level as in Fig. 3a, after 2 months of tyrosine kinase inhibitors (TKI) treatment shows multiple foci of increased bone density within the vertebral bodies (arrows) and sternum. As the patient responded to TKI, this was considered as a flare phenomenon.
rarely observed during treatment with crizotinib in 1–2% of patients [35]. The possible relationship between pneumonia and crizotinib should be investigated on a case-by-case basis because often related to progression, infection or radiotherapy [36]. Interstitial pneumonia following treatment with crizotinib is a much rarer event, and is sometimes fatal.

Several cases of pneumothorax secondary to significant necrosis of tumor tissue adjacent to the pleura have been reported [37]. It is considered to be due to the rapid lysis and then necrosis of tumor tissue, which causes the pleura to rupture or occurrence of a bronchopleural fistula.

Revised RECIST criteria

Acquired resistance to crizotinib is frequent and due to the selection of tumor clones that are less sensitive to the drug. Various clinical scenarios of disease progression have been observed: rapid symptomatic progression; single new lesion or increased size of a single lesion that was previously under control (oligoprogression); slow asymptomatic growth of multiple lesions that were formerly controlled. Disease flare-up, as described following EGFR TKI discontinuation, has not been studied systematically, but two cases of flare-up have been reported upon discontinuation of crizotinib [38,39].

Continuing treatment with crizotinib after disease progression according to RECIST 1.1 is associated with a significant increase in the overall survival of patients after progression (16.4 months vs. 3.9 months, \( P < 0.0001 \)) and initiation of treatment (29.6 months vs. 10.8 months, \( P < 0.0001 \)) [39]. For this reason, it is recommended to continue treatment in patients with oligometastatic progression who could benefit from localized treatment (radiotherapy, radiofrequency ablation, or surgery) and in patients with progression according to RECIST but ongoing clinical benefit. The decision to discontinue treatment should not therefore be entirely based on progression according to RECIST [40].

**ROS1 gene rearrangement**

ROS1 rearrangement occurs in 1–2% of NSCLC cases and is predominantly observed for adenocarcinomas, in women and nonsmoking patients [41]. Crizotinib shows some efficacy on ROS1 rearrangement tumors with an objective response rate of 72%, and only 10% of non-controlled disease at 8 weeks [42].

**Angiogenesis inhibitors**

Bevacizumab is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody. It is used as part of a combination chemotherapy regimen or in combination with a TKI, in patients with non-squamous NSCLC. Lung-related contraindications are histology showing squamous NSCLC, excavated tumors and significant contact between the tumor and main vessels [43]. Other contraindications are: a history of bleeding especially hemoptysis or a history of thrombosis such as stroke, ischemic or congestive heart disease, and digestive perforation.

**Pulmonary complications**

The main and sometimes fatal risk is pulmonary hemorrhage, which was reported in 5% of the patients of the initial trials that included squamous tumors [44]. The meticulous identification of risk factors for hemoptysis resulted in the exclusion from treatment of patients with squamous NSCLC, excavated tumors and tumors with significant contact (>180°) with a main mediastinal or central vessel [45]. This reduced the occurrence of this serious complication. Reck et al. [46] provided expert recommendations on the use of bevacizumab, and emphasized two formal contraindications: histology showing squamous NSCLC and/or a history of hemoptysis (>2.5 mL). However, not clinical or radiological data (including cavitation or central localization) are available to help anticipate the occurrence of hemoptysis after initiation of bevacizumab [44] (Fig. 4). This increased risk of hemorrhage with squamous tumors has not been reported with ramucirumab [47], which is pending marketing authorization for use as second-line treatment of NSCLC, whatever the histology subtype.

Tumor necrosis with cavitation was described in 14 out of 72 (19%) cases of NSCLC treated with bevacizumab in combination with standard chemotherapy [48]. For proximal tumors, cavitation is a risk factor for hemoptysis or bronchopleural fistula [49,50].

**Revised RECIST criteria**

It has been suggested that cavitation, which is frequently observed with bevacizumab, be taken into account. To do this, Crabb et al. [51] proposed that the larger diameter of the cavity be subtracted from the larger diameter of target lesions, resulting in a change to how the response and progression would be assessed. However, the relevance of this proposition remains to be confirmed (Fig. 5).

**Immunotherapy**

The very recently introduced drugs of this new therapeutic class seem promising in patients with NSCLC [52,53]. Ipilimumab is an activator of cytotoxic T cells and has been shown to improve the overall survival of melanoma patients, as have the anti-programmed cell death-1 (anti-PD1) and anti-programmed cell death ligand-1 (anti-PD-L1) antibodies in late-stage melanoma. Clinical trials on populations of lung cancer patients are currently underway, notably with the anti-PD1 and anti-PD-L1 antibodies.

CTLA4 and PD1 are the main targets of treatment strategies aimed at co-stimulating the cell-mediated immune response. Activated recirculating T cells are targeted by modulation via CTLA4, and tissue-infiltrating T cells are targeted by PD1 modulation. PD1 blockade with an anti-PD1
antibody results in compartmentalization of the immune and inflammatory response within tissue. Since the original report by Brahmer et al. [54], several studies have confirmed the effectiveness of this therapeutic approach for treating NSCLC [55].

Currently ongoing studies aimed at evaluating the use of tissue markers to predict a therapeutic response, such as the expression of PD-L1 by tumor cells as determined by immunohistochemistry, are yet to produce conclusive results. Trials on the use of six drugs for lung cancer are currently underway and so far the randomized comparison of nivolumab to chemotherapy revealed that it practically doubles the overall survival at 2 years [55].

Toxicity

The toxicity related to immunotherapy is mainly due to reactions the mimic autoimmune conditions. Such conditions can affect the digestive system (enterocolitis mimicking Crohn disease), liver, skin (vitiligo), lungs (interstitial lung disease), lymph nodes (sarcoidosis-like infiltration), hypophysitis, thyroiditis [56,57].

Systemic imaging findings of toxicity related to immunotherapy have been reported. They mimic autoimmune conditions and may be associated with a greater efficacy of treatment as suggested by Bronstein et al. in 119 melanoma patients treated with ipilimumab [58]. Metastasis was controlled in 55% of patients in the group with systemic imaging abnormalities related to immunotherapy versus 10% in the group without systemic imaging abnormalities. The imaging findings were variable in nature. They were sometimes clinically obvious (colitis, hypophysitis, arthritis, thyroiditis) but sometimes clinically occult with benign lymph node enlargement (often sarcoidosis-like), myositis or infiltration of abdominal fat. Interstitial lung disease was observed with an incidence of 3% in studies comparing nivolumab to docetaxel, and was severe (grades 3–4) in 1% of treated patients.

Influence on post-therapeutic evaluation

Immunomodulators and immune checkpoint inhibitors lead to tumor regression but can also potentially increase inflammatory cell infiltration [59]. The radiological evaluation of patients treated by immunotherapy should therefore take this into account [60].

The immune reaction driven by immunotherapy may causes inflammatory cells to flock around the target lesions, thus increasing the size of both target and non-target lesions, even the appearance of new lesions (Fig. 6) [61,62]. Such changes mimic tumor progression according to RECIST 1.1 criteria prior to a decrease in lesion size. New immune-related response criteria (irRC) have been proposed to take into account the specificities of immunotherapy [63]. Four patterns of tumor response to immunotherapy have been described:

• regression of the initial lesions without appearance of new lesions;
• unchanged tumor burden but followed by a slow, continuous regression of the overall tumor burden in some patients;
• regression of lesions after an initial increase of the overall tumor burden (flare);
regression of initial lesions associated with the appearance of new lesions [64].

To take into account such changing clinical pictures during treatment, irRC criteria:
- include a confirmation of progression by repeat evaluation no less than 4 weeks after the first potential evidence of progression;
- recognize that the appearance of new lesions during immunotherapy should not be considered as progression but that the new lesions should be added to the sum of originally identified lesions when evaluating the tumor burden.

There are many limitations to the irRC criteria: the bidimensional measurements they are based on are in line with WHO criteria, but are now rarely used in clinical studies and are replaced by the unidirectional measurement of the larger axis of target lesions (RECIST 1.0 and 1.1). Such bidimensional measurements introduce a greater variability than unidirectional measurements and make it difficult to compare the responses with studies using the RECIST criteria. Nishino et al. suggested that the irRC criteria be revised into new immune-related RECIST 1.1 (irRECIST 1.1) (Table 2) criteria based on unidirectional measurements and including other quantifiable measurements such as tumor density, volume, and metabolic activity [60]. Prospective studies will be required to validate these criteria and their use for the evaluation of overall survival.

**Conclusion**

Targeted therapy is more and more frequently used to treat NSCLC patients due to its higher therapeutic efficacy and better clinical tolerance. Besides the need for appropriate tissue sampling to select eligible patients by determining

<table>
<thead>
<tr>
<th>Table 2</th>
<th>irRC and irRC RECIST 1.1 (modified from ref. [61]).</th>
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<tbody>
<tr>
<td><strong>irRC criteria</strong></td>
<td><strong>Suggested revision of irRC RECIST 1.1</strong></td>
</tr>
<tr>
<td>Measurable lesions</td>
<td>≥ 5 × 5 mm</td>
</tr>
<tr>
<td>Number of targets</td>
<td>Up to 5 per organ, up to 10 digestive and 5 skin targets</td>
</tr>
<tr>
<td>Target measurement</td>
<td>Larger diameter × largest perpendicular diameter (cm²)</td>
</tr>
<tr>
<td>Sum of measurements</td>
<td>Sum of bidimensional measurements for targets and newly occurring lesions</td>
</tr>
<tr>
<td>Evaluation of target lesion response</td>
<td>PD: ≥ 25% compared with nadir</td>
</tr>
<tr>
<td>PR: ≥ 50% decrease compared with initial evaluation</td>
<td></td>
</tr>
<tr>
<td>CR: complete disappearance of all targets</td>
<td></td>
</tr>
<tr>
<td>New lesions</td>
<td>Not considered as progression</td>
</tr>
<tr>
<td>Confirmation</td>
<td>Confirmation of CR, PR or PD by repeat evaluation no less than 4 weeks after 1st evaluation</td>
</tr>
<tr>
<td>Larger diameter ≥ 10 mm (except for lymph nodes: smaller diameter ≥ 15 mm)</td>
<td></td>
</tr>
<tr>
<td>Up to 2 per organ, and 5 in all</td>
<td></td>
</tr>
<tr>
<td>Larger diameter (except for lymph nodes: small diameter)</td>
<td></td>
</tr>
<tr>
<td>Sum of diameters for targets and newly occurring lesions</td>
<td></td>
</tr>
<tr>
<td>PD: ≥ 20% compared with nadir</td>
<td></td>
</tr>
<tr>
<td>CR: complete disappearance of all targets and lymph nodes ≤ 10 mm</td>
<td></td>
</tr>
<tr>
<td>Not considered as progression</td>
<td></td>
</tr>
<tr>
<td>Confirmation of CR, PR or PD by repeat evaluation no less than 4 weeks after 1st evaluation</td>
<td></td>
</tr>
</tbody>
</table>

irRC: immune-related response criteria; irRECIST 1.1: immune-related RECIST 1.1; CR: complete response; PR: partial response; PD: progressive disease.
the molecular abnormalities that can be targeted, specific patterns of response and toxicity are associated with these cytostatic agents. Radiologists responsible for the post-therapeutic evaluation of patients based on RECIST 1.1 criteria for standard chemotherapy, should also be familiar with the specific thoracic complications related to these treatments and the revised evaluation criteria (such as irRC or irRECIST 1.1 criteria) intended to modulate the interpretation of CT scans (Table 3). Finally, radiologists should also bear in mind that the decision to continue treatment does not depend solely on the evaluation of tumor response (typically according to RECIST 1.1), but includes other parameters such as patient tolerance, clinical benefit and alternative treatment options.

Disclosure of interest

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ACT: personal fees for educational support or advisory support: Boehringer Ingelheim, Lilly.
DMS: personal fees for educational support or advisory support: Roche SAS, Eli Lilly, Astra Zeneca, Novartis, Pfizer, Boehringer Ingelheim, Amgen, BMS.

References


Table 3 Thoracic adverse effects and revised RECIST 1.1 criteria for the different targeted treatment categories.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Thoracic adverse effect</th>
<th>RECIST 1.1 revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation TKI</td>
<td>Interstitial lung disease (1—5.5%) Pneumothorax Flare-up upon sudden discontinuation Osteoblastic bone reactions often associated with favorable outcome</td>
<td>None, but continuation of treatment after progression per RECIST 1.1 if ongoing clinical benefit</td>
</tr>
<tr>
<td>TKI (Crizotinib®)</td>
<td>Interstitial lung disease Pneumothorax</td>
<td>None, but continuation of treatment after progression per RECIST 1.1 if ongoing clinical benefit</td>
</tr>
<tr>
<td>Antiangiogenic (Avastin®)</td>
<td>Massive tumor necrosis Hemoptyisis Bronchopleural fistula Increase in lesion size and appearance of new lesions during treatment secondary to infiltration of immune cells</td>
<td>Subtract tumor necrosis area from measurement for RECIST evaluation. Not validated Immune-related response criteria (irRC) Immune-related RECIST 1.1 (irRECIST 1.1)</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td></td>
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TKI: tyrosine kinase inhibitors; irRC: immune-related response criteria; irRECIST 1.1: immune-related RECIST 1.1.


