Patterns of responses in metastatic NSCLC during PD-1 or PDL-1 inhibitor therapy: Comparison of RECIST 1.1, irRECIST and iRECIST criteria


Keywords: Carcinoma; Non–small cell lung cancer; Immunotherapy; Imaging evaluation

Abstract: Background: Immune checkpoint inhibitors are an important tool in the therapeutic strategy against metastatic non–small cell lung cancer (NSCLC); however, radiological evaluation is challenging due to the emergence of atypical patterns of responses. Several evaluation criteria have been proposed, such as the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, immune-related RECIST (irRECIST) and iRECIST, but have not been systematically compared in a homogeneous population.

Patients and methods: We conducted a monocentric retrospective analysis of consecutive advanced NSCLC patients treated with an anti–programmed cell death-ligand 1. Response patterns and the discordance between RECIST 1.1, irRECIST and iRECIST guidelines were described, and associations of response patterns and clinical outcome were explored.

Results: Overall, 160 patients treated between February 2013 and October 2016 were included. Atypical responses were observed in 20 patients (13%), including eight pseudoprogressions (PsPDs) (5%) and 12 dissociated responses (8%). Thirteen of the 20 patients demonstrated clinical benefit. Per the RECIST 1.1, 37 patients (23%) showed an objective response or stable disease, and 123 patients (77%) exhibited progression. Eighty progressive patients were assessable for irRECIST and iRECIST: 15 patients were assessed differently; however, only three (3.8%) mismatches with a theoretical impact on the therapeutic decision were identified.
Patients with PsPD or dissociated response had higher overall survival than patients with true progression.

**Conclusion:** Atypical responses (PsPD/dissociated response) occurred in 13% of NSCLC patients under immune checkpoint inhibitors. Based on survival analyses, the RECIST 1.1 evaluation underestimated the benefit of immune checkpoint inhibitors in 11% of the progressive patients. Immune-related RECIST and iRECIST identified these unconventional responses, with a 3.8% discrepancy rate.

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1. **Introduction**

As the most common cancer type across the globe [1], lung cancer is now the leading cause of cancer death worldwide. Immune checkpoint inhibitors targeting programmed cell death-1 (PD-1) or programmed death-ligand 1 (PD-L1) have become an important treatment avenue for metastatic lung cancer [2–6], resulting in increased overall survival (OS) compared with standard chemotherapy [7–12]. Since 2015, nivolumab, pembrolizumab and recently atezolizumab, have been approved by the US Food and Drug Administration for the treatment of non–small cell lung cancer (NSCLC), irrespective of the histologic subtype after first-line therapy, whereas pembrolizumab is also authorised as first-line therapy in patients with PD-L1 overexpression (>50%) [13].

Nevertheless, response patterns of tumours treated with immunotherapies may differ compared with conventional chemotherapeutic agents or targeted therapies, and accurate assessment of the response can be radiologically challenging [14]. Initially described in metastatic melanomas treated with ipilimumab [15], immune-related response patterns such as an initial increase in tumour burden or the appearance of new lesions termed ‘pseudoprogression’ may lead to misinterpretation of the patient’s status and by consequence generate suboptimal clinical decisions [16]. As there are no reliable clinical or biological markers of activity for immune checkpoint inhibitors, radiological evaluation plays a leading role in decision-making care [17].

Conventional radiological response criteria, the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, [18] are insufficient for capturing pseudoprogression (PsPD) and can result in underestimation of the therapeutic benefit of immune checkpoint blockade. Several radiological criteria have been developed specifically for immunotherapy to better define the tumour response. Two-dimensional immune-related response criteria (irRC) were proposed in 2009 [15]. A simplification of these criteria was proposed in 2013, irRECIST (immune-related) [19–22]. More recently, the RECIST working group published a proposition of new criteria called iRECIST, to standardise response assessment among immunotherapy clinical trials [23].

The objectives of the present study are to describe the response patterns and the differences between RECIST 1.1, irRECIST and iRECIST criteria assessments in a homogeneous population of advanced NSCLC patients treated with anti-PD-1 or anti-PD-L1 therapy.

2. **Materials and methods**

2.1. **Study design**

A retrospective analysis of all consecutive patients receiving anti-PD-1 or anti-PD-L1 agents for advanced NSCLC after failure of first-line chemotherapy, was conducted at the Gustave Roussy, France between February 2013 and October 2016. Informed consent was obtained from all patients, and the local ethics committee approved the protocol. Patients with a concomitant second cancer, who had received concomitant radiation therapy or intrathecal therapy, or without adequate computed tomography (CT) evaluation (absence of confirmatory CT after initial progression or no target lesions on baseline CT imaging) were excluded. Follow-up scans were performed periodically according to study protocols or clinical routine (mostly every 6 weeks); anticipated CTs for clinical deterioration were analysed.

2.2. **Patterns of responses**

Stable disease (SD), partial responses (PRs) and complete responses (CRs) were identical for all guidelines. For progressing patients evaluated per the RECIST 1.1, PsPD was defined as a decrease or stabilisation of the tumoral elements that had constituted an initial assessment of progression, and dissociated responses were defined as concomitant decrease in certain tumoral elements and increase in other elements. Clinical benefit was defined as patients receiving at least 6 months treatment.

2.3. **Tumour response assessment per RECIST 1.1, irRECIST and iRECIST (Table 1)**

Two radiologists, specialised in immunotherapy evaluation (1 senior, 1 junior), centrally reviewed all consecutive CT scans to reach a consensus. At baseline, the
sums of the longest diameters of target lesions (maximum five measurable target lesions \( \geq 10 \) mm, maximum two per organ) and non-target lesions were determined, following the RECIST 1.1 guidelines [18].

The three guidelines have identical definitions of CR, PR and SD but differ in cases of progression. Unlike the RECIST 1.1 guidelines, irRECIST and iRECIST require a confirmatory CT at 4–8 weeks, and death or immunotherapy discontinuation due to clinical progression is considered as confirmation of progression.

For appearance of one or more new lesion(s), the site and size were recorded. New measurable lesions were added to the sum of target lesions according to the irRECIST guidelines but were evaluated separately according to the iRECIST guidelines. To confirm progression, the irRECIST guidelines require an increase of target, non-target or new lesions compared with nadir in the subsequent CT without a clear cut-off. If progression was not confirmed, the baseline was reset to the date of suspected progression only for the irRECIST evaluation [19,20].

According to the iRECIST guidelines, suspicion of progression was recorded as immune unconfirmed progressive disease (iUPD). Confirmed PD was defined as an additional increase in the size of target lesions, additional qualitative worsening of non-target lesions, an increase in the sum of new measurable target lesions \( >5 \) mm, qualitative worsening of non-measurable new lesions or the appearance of new lesions. If progression was not confirmed, the response status was evaluated

<table>
<thead>
<tr>
<th>Table 1 Summary of RECIST, irRECIST and iRECIST Criteria.</th>
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<td><strong>RECIST 1.1</strong></td>
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<td><strong>Target and non-target lesions</strong></td>
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<td><strong>New lesion</strong></td>
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<td><strong>Confirmed PD</strong></td>
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CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; iUPD, unconfirmed progressive disease; iCPD, confirmed progressive disease; LD, longest diameters; TMTB, total measured tumour burden.
compared with baseline or nadir as iCR, iPR, iSD or iUPD [23].

2.4. Statistical analyses

OS was estimated according to the Kaplan–Meier method and survival curves were compared using the log-rank test using SAS statistical software.

3. Results

3.1. Patient characteristics

Among the 182 consecutive NSCLC patients treated, 160 were eligible. Twenty-two patients were excluded, 13 due to the absence of confirmatory CT, three for intrathecal and/or radiation therapy of brain metastases, three for non-evaluable lesions, two for discontinuation unrelated to progression after the first occurrence of progression (one stroke and one allergic pneumonitis) and one progression of concomitant prostate cancer. Patient characteristics are shown in Table 2. Median age was 66 years (range 32–87). Most patients had adenocarcinoma (63%) or squamous (30%) histology. Anti-PD-1 (nivolumab and pembrolizumab) were the most common treatments (64%) and 34% had received an anti-PD-L1 (atezolizumab and durvalumab).

3.2. Treatment characteristics and outcome

Median OS was 11.3 months (range 0.7–51.2), median follow-up was 8.2 months (0.7–51.2), and 29 patients were ongoing at the time of the analysis. Of the 160 patients, 37 (23%) had the following: CR (1 patient), PR (16 patients) and SD (20 patients) according to all three guidelines. Two of these 37 patients discontinued immunotherapy within 6 months, one for toxicity and the other due to death unrelated to progression.

Seventy-seven patients (48%) had initial progression (at the first CT evaluation), which was confirmed by a subsequent CT 4–8 weeks later or by death related to tumour progression in 25 patients. Twenty-six patients (16%) progressed after the first CT evaluation, following stability in 21 patients or PR in five patients. Median time to progression in these patients was 4.3 months (range 1.4–26.6). Fig. 1 shows OS according to best overall response per the irRECIST and iRECIST.

3.3. Atypical responses

Atypical responses were observed in 20 (13%) of the 160 patients, including eight PsPD (5%) and 12 dissociated responses (7.5%) (Fig. 2). These patients had a significantly longer median OS than patients with confirmed progression, 9.8 months (range 3.5–33.6) versus 6.1 months (range 0.7–51.2), respectively (p < 0.0001). With 13 patients receiving treatment for more than 6 months, 11% (13/120) of the patients initially characterised as PD by the RECIST 1.1, were deemed as having clinical benefit.

3.3.1. Pseudoprogression

Median time to PsPD was 10.2 weeks (2.3–84), including two late PsPD after 12 weeks. Of these eight patients, seven received PD-1 inhibitors (six nivolumab and one pembrolizumab) and one received a PD-L1 inhibitor (atezolizumab). Two patients had complete regression of new lesions. A 72-year-old female treated with atezolizumab had stability in an initial lung lesion at the first assessment but a qualitative increase of carcinomatous lymphangitis and peritoneal carcinomatosis, with new lung metastases (week 4). Complete

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (%) (n = 160)</th>
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<tbody>
<tr>
<td>Age in years, median (range)</td>
<td>66 (32–87)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98 (61%)</td>
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<tr>
<td>Female</td>
<td>62 (39%)</td>
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<tr>
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<tr>
<td>Current</td>
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<tr>
<td>Former</td>
<td>84 (53%)</td>
</tr>
<tr>
<td>Never</td>
<td>19 (12%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Histology</td>
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</tr>
<tr>
<td>Adenocarcinoma</td>
<td>100 (63%)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>49 (30%)</td>
</tr>
<tr>
<td>Other</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>103 (64%)</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>27 (17%)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Necitumumab + pembrolizumab</td>
<td>16 (10%)</td>
</tr>
<tr>
<td>Other combination</td>
<td>4 (2%)</td>
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</tbody>
</table>

Fig. 1. Kaplan–Meier overall survival estimates. In pink, conventional stable disease, partial and complete responses (n = 37); in green, true progressors (n = 103) and in orange, atypical responses (n = 20). CR, complete response; PR, partial response; SD, stable disease; atypical, atypical responses. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
regression was seen at week 15 with a CR achieved at week 50, which was ongoing at week 136 (Fig. 3A). A 71-year-old male treated with nivolumab had a new subcentimetric solid pleural nodule after 8 weeks of treatment, with complete regression after 8 weeks.

Fig. 3B shows another example of early PsPD on target and non-target lesions in a 69-year-old patient treated with nivolumab. Despite clinical improvement, a 133% increase in the total tumour burden was seen at the first assessment (week 4) and an increase of non-target carcinomatous lymphangitis. In the CT at week 12, tumour burden had decreased by up to 20% and the carcinomatous lymphangitis had regressed. The patient ultimately presented with new progression based on the appearance of retroperitoneal lymph nodes and died after 1 year of treatment.
3.3.2. Dissociated responses

We observed 12 dissociated responses, six (50%) presenting with clinical benefit. A 54-year-old patient treated with pembrolizumab experienced a dissociated response at week 7, with a reduction in the size of adrenal lesions with concomitant increases in a primary mass and a peritoneal lesion (Fig. 4A). Another example of dissociated response was seen at week 13 in a

Fig. 3. Representative imaging of two patients experiencing early PsPD. (A) PsPD of carcinomatous lymphangitis, peritoneal carcinomatosis and lung metastasis. (B) PsPD of carcinomatous lymphangitis and lung lesions.
60-year-old female treated with nivolumab who experienced an adrenal lesion decrease, with a concomitant increase of the primary mass and mediastinal lymph node (Fig. 4B). Four patients presented new lymph node lesions with a concomitant reduction in the size of the target lesions, and one patient had a dissociated response in pulmonary lesions.

3.4. Comparison of the RECIST, iRECIST and irRECIST criteria at the first occurrence of progression

A total of 123 patients presented with suspicion of progression during the study, with a median time to progression of 1.7 months (range 0.4–29.5). Among them, 43 patients had PD confirmed by either death relating to tumoural evolution (n = 31) or treatment discontinuation related to clinical deterioration (n = 12), and 80 patients were assessable according to imaging criteria.

Among the 80 confirmatory CTs (Table 3), there were 15 discordant assessments between the irRECIST and iRECIST, of which three (3.8%) could have had a theoretical impact on the therapeutic decision. These three patients had confirmed PD by the irRECIST, but not by the iRECIST (which identified them as iUPD, allowing treatment continuation). During follow-up, all

Fig. 4. Examples of two patients with dissociated responses. (A) Dissociated responses of adrenal, lung and peritoneal lesions. (B) Dissociated responses of adrenal, lymph node and lung lesions.
three ultimately experienced progression and died within 6 weeks.

For 17 patients, progression was not confirmed according to both the irRECIST and iRECIST criteria; nine were identified as SD according to the irRECIST and iUPD per the iRECIST, three as SD according to the irRECIST and iPR per the iRECIST and five patients were identically identified as SD and iSD (n = 4) or PR and iPR (n = 1), respectively.

These 17 patients met the definition of atypical responses corresponding in imaging to seven PsPD and 10 dissociated responses. Ultimately, 13 patients met the definition of clinical benefit, giving an 11% (13 of 120) rate of treated patients who were characterised as PD by the RECIST criteria, but who had treatment benefit. Of the 60 patients with PD confirmed by both irRECIST and iRECIST, three (5%) had an atypical response on imaging (all dissociated responses) not recognised by the criteria, according to the definition of the initial target lesions.

4. Discussion

In this retrospective analysis of CT images of NSCLC patients treated with anti-PD-1 or anti-PD-L1 therapy, we have described atypical patterns of response and compared the RECIST 1.1, irRECIST and iRECIST radiological criteria. Patients with atypical responses (PsPD or dissociated responses), according to the iRECIST and irRECIST, represent 11% of the RECIST (PsPD or dissociated responses), according to the iRECIST and irRECIST, represent 11% of the RECIST 1.1 so-called progressive patients and had superior OS compared to patients with true disease progression. This suggests that the RECIST 1.1 underestimates the benefits of PD-1 or PD-L1 inhibitors in approximately 11% of the evaluated population. PsPD is now a well-documented phenomenon, characterised by response or stability after an initial increase of tumour burden or a reduction in total tumour burden, despite the appearance of new lesions [14–16]. In our population, 5% (8/160) of patients experienced PsPD, most of them were treated with PD-1 inhibitors, similar to rates reported in clinical trials with nivolumab or pembrolizumab in NSCLC. In a phase I study of nivolumab in advanced NSCLC, 5% (6/129) of the patients experienced PsPD [8]. In the recent meta-analysis of Kazandjian et al., 420 patients had progression; of whom 121 received treatment after RECIST progression and 10 ultimately exhibited a PR. Stable patients and occurrence of dissociated responses were not described. The proportion of patients treated beyond RECIST progression in our study was high (around 90%) compared with approximately 30% in other studies [24–28].

PsPD has been reported in other cancer types; recent data in metastatic melanoma revealed 6.7–10% PsPD [14,15,26,27], and Escudier et al. [28] reported a cohort of 316 progressive renal cancer patients, of whom 153 were treated after RECIST progression, with ultimately 31 PR/CRs and 51 SD (26%). In our study, all patients with PsPD showed clinical benefit with at least 6 months of treatment, including an ongoing CR lasting more than 34 months while on therapy.

Dissociated responses are another unconventional immune-related response pattern, which suggest different responses across organs. However, few data are available, mostly due to the fact that this profile is difficult to pick up by conventional RECIST assessment, requiring deep analysis of CT images. In this study, existing adrenal lesions appeared more responsive to therapy, in accordance with a recent study by Nishino et al. [29] in advanced NSCLC with a PD-1 inhibitor.

Comparing the three criteria (RECIST 1.1, irRECIST and iRECIST), as expected, the only potentially different assessment outcomes were seen with progressive patients, given that the definition of SD, PR and CR is the same for all the three. According to the RECIST, progression of target and/or non-target lesions and/or the appearance of new lesion(s) defines progression, whereas it requires confirmation per the irRECIST and iRECIST. The assessments according to the irRECIST and iRECIST were highly concordant in this study. The majority of mismatches between the two criteria concerned iSD and iUPD, which is a new category of response proposed by the iRECIST allowing treatment continuation. Of the 80 radiologically assessable patients, there were only three (3.8%) true mismatches with theoretical impact on the therapeutic decision, where iRECIST interpretation as iUPD has led to unnecessary continuation of treatment.

The main differences between the irRECIST and iRECIST guidelines rely on the addition of new lesion(s) into the sum of initial target lesions, which jeopardise the possibility of clearly understanding the different patterns of PsPD. The occurrence of new measurable lesions has the same interpretation per the iRECIST as an increase in existing lesions. Moreover, irRC (and subsequently irRECIST) propose proceeding by resetting baseline as the date of suspicion of progression in cases when the suspicion was not confirmed (i.e. retrospectively), leading to many misunderstandings in data interpreted with irRC/irRECIST. Finally, no clear definition of confirmation of progression was released, leaving the radiologist and the clinician stranded when
dissociated responses or relative stabilisations were observed [30]. Taking this into account, the RECIST Working Group proposed new guidelines to homogenise data collection across clinical trials evaluating immuno-therapeutic agents. In routine practice, for oncology-focused radiologists, the iRECIST criteria are far easier to work with, rather than irRC or irRECIST [31].

Our study has some limitations. First, it was carried out in NSCLC patients alone and in the ones who were treated in a single centre, and more data are needed to confirm the proportion of PsPD and dissociated patterns of responses to extrapolate these results to the wider NSCLC population and other tumour types. In addition, the retrospective nature of the study gives non-homogeneous CT methodology, performed according to different study protocols or clinical routine, and anticipated evaluations before the first scheduled CT were required in some cases due to intercurrent events related to clinical progression (abdominal pain, dyspnoea, etc.). Finally, more data are needed to compare the RECIST, iRECIST and irRECIST to quantify the differences in outcome estimation.

In conclusion, progressive NSCLC patients under immune checkpoint inhibitors may experience atypical responses (PsPD or dissociated response), which are not captured by the RECIST 1.1 criteria. IrRECIST and iRECIST demonstrated an improved capacity to capture these unconventional responses, with a 3.8% disagreement. Based on survival analyses, conventional RECIST 1.1 evaluation underestimates the benefit of immune checkpoint inhibitors in 11% of progressive patients.

Conflict of interest statement

None declared.

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References


