Pseudoprogression in Non–Small Cell Lung Cancer upon Immunotherapy: Few Drops in the Ocean?

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During checkpoint blockade immunotherapy, some patients with cancer may experience an initial progression followed by a long stabilization (stable disease) or durable response. This phenomenon is commonly known as pseudoprogression and was first described in 9.7% of patients with melanoma who were treated with ipilimumab in phase II studies.[1] A retrospective analysis of the phase I trial Keynote 001 identified pseudoprogression in 7% of patients with melanoma treated with pembrolizumab.[2] A subsequent pooled analysis of two phase III studies (CheckMate 066 and CheckMate 067) reported pseudoprogression in 4.6% of patients with melanoma treated with nivolumab.[3] Similarly, a retrospective analysis of a phase II trial testing nivolumab in renal cell carcinoma[4] and two exploratory analyses[5,6] of CheckMate 025[7,8] (a phase III trial comparing nivolumab to everolimus in pretreated patients with renal cell carcinoma) reported pseudoprogression in 7% and 1% to 5% of patients, respectively. Of note, there is currently no consensus on the definition of pseudoprogression, and the percentage of patients with pseudoprogression can be reported differently in the literature, either relative to the whole population receiving treatment or restricted to the patients with progression (treated or not treated beyond progression).

The article by Fujimoto et al.[9] in this issue of the *Journal of Thoracic Oncology* addresses this important and clinically relevant topic among patients with NSCLC. Although retrospective, the study has the merits of being multicentric (15 centers), large (542 patients), and having been conducted in a real-word setting. Fujimoto et al.[9] have defined pseudoprogression as a Response Criteria in Solid Tumors (RECIST)-defined response occurring after RECIST-defined progression with a decrease in the sum of the longest diameter of the target lesions by at least 30% from the time of determination of disease progression rather than from baseline. They observed pseudoprogression in 14 of 542 patients (3%) with NSCLC treated with anti–programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) agents and in 5% of progressing patients.

The study highlights the fact that the initial progression in patients with pseudoprogression appears very early after the first injection (median time 1 month [reported as median progression-free survival 1]) compared with the median time of 2.4 months according to computed tomography (CT) evaluation. One can speculate that in patients who present a partial response (PR), a systematic CT scan at 1 month would probably

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Disclosure: Dr. Champiat has received honoraria from Amgen, AstraZeneca, BMS, Janssen, MSD, Novartis, and Roche. As part of the Drug Development Department of Institut Gustave Roussy, Dr. Champiat is subinvestigator of clinical trials for AbbVie, Agios Pharmaceuticals, Amgen, Argen-X BVBA, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca, Aveo, Bayer Healthcare AG, BBB Technologies B.V., Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Daiichi Sankyo, Debiopharm S.A., Eisai, Eli Lilly and Company, Exelixis, Forma, Gamamabs, Genentech, Inc., GlaxoSmithKline, H3 Biomedicine, Inc., Hoffmann La Roche AG, Innate Pharma, Iris Servier, Janssen Cilag, Kyowa Kirin Pharmaceutical Development, Inc., Loxo Oncology, Lytix Biopharma AS, Medimmune, Menarini Ricerche, Merck Sharp and Dohme Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Octimet Oncology NV, Oncoethix, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, Pharma Mar, Pierre Fabre, Roche, Sanofi Aventis, Taiho Pharma, Tesaro, Inc., and Xencor. Also as part of the Drug Development Department of Institut Gustave Roussy, Dr. Champiat has received research grants from AstraZeneca, BMS, Boehringer Ingelheim, Janssen Cilag, Merck, Novartis, Pfizer, Roche, and Sanofi and nonfinancial support (drugs supplied) from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Johnson and Johnson, Eli Lilly and Company, Medimmune, Merck, NH TherAGuiX, Pfizer, and Roche. Dr. Besse reports performing research at Institut Gustave Roussy that was sponsored by AbbVie, Amgen, AstraZeneca, Biogen, Blueprint Medicines, BMS, Celgene, Eli Lilly and Company, GSK, Ignyta, IPSEN, Merck KGaA, MSD, Nektar, Onxeo, Pfizer, PharmaMar SA, Sanofi, Spectrum Pharmaceuticals, Takeda, and Tiziana Pharma outside the submitted work. The remaining authors declare no conflict of interest.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2018.12.011

have found more asymptomatic pseudoprogression. Additionally, the half-life of nivolumab is very long (around 26 days). Thus, some patients with early progression during immunotherapy might be qualified as responders to a subsequent treatment even though they are actually experiencing a pseudoprogression. This might explain why the rate of response to first systemic treatment after nivolumab was 16.2% in 319 patients when a response rate of 9% is expected for docetaxel in this setting.[10] Altogether, this suggests that the rate of pseudoprogression might have been underestimated in this study. Unfortunately, these limitations also apply to the other reports on pseudoprogression, in particular, to retrospective studies that do not have confirmatory CT for all evaluated patients.

On the other hand, there is a second hypothesis suggesting that the rate of pseudoprogression may have been overestimated in this study. Previous data from two phase III trials (CheckMate 017[5] and CheckMate 057[6]) and from a phase I trial[11] showed an unconventional pattern of benefit in 3% to 5% of patients with NSCLC who were treated with nivolumab. Nevertheless, the heterogeneity of the criteria used for the definition of atypical response in these studies did not allow identification of the exact percentage of patients with pseudoprogression. In CheckMate 063, a phase II trial of nivolumab in pretreated squamous cell lung carcinoma[12] and in a retrospective analysis of the OAK study (a phase III trial of atezolizumab in pretreated NSCLC[13]), a 30% or greater reduction in target lesions after initial progression according to RECIST (pseudoprogression) was observed in 1.7% and 1.6% of patients, respectively. A small retrospective study that included 56 patients with NSCLC treated with nivolumab reported no pseudoprogression, defined as an increase in tumor burden followed by subsequent response,[14] whereas two larger analyses including 535 and 166 patients with NSCLC treated with an anti–PD-1/PD-L1 agent[15,16] showed a 30% or greater reduction in target lesions after initial progression according to RECIST (pseudoprogression) in approximately 2% of patients.

All these data highlight the fact that responses after initial progression upon treatment with immune checkpoint inhibitors (ICIs) are uncommon in patients with NSCLC, and as suggested by Fujimoto et al.,[9] up to 95% of patients treated beyond progression with immune checkpoint blockade do not experience any subsequent responses. In addition, the median progression-free survival 2, defined as the time to second progression according to RECIST or death, was significantly lower in patients with pseudoprogression than in responding (progression-free) patients (7.3 months versus not reached, [$p < 0.001$]), suggesting that the effect of immune checkpoints blockade in patients with pseudoprogression is not only delayed but also short-lasting. In this regard, few studies have included a prolonged stabilization after initial progression according to RECIST in the definition of pseudoprogression. In two retrospective series,[17,18] patients with responses (complete response or PR) or stabilization for more than 6 months after initial progression according to RECIST were defined as pseudoprogressors and the overall rate of pseudoprogression was 5%. This percentage is very close to the frequency of pseudoprogression in studies in which only responses (complete response and PR) after progression according to RECIST were considered in the definition. Interestingly, in Checkmate 063[17] and in a post hoc analysis of the OAK study,[18] patients with prolonged stabilization after initial progression according to RECIST comprised 8% and 19.5% of the whole study populations, respectively. The lack of a fixed time cutoff to define the period of stability after progression according to RECIST may explain these discrepant results. In fact, in Checkmate 063[12] and the OAK study,[13] patients with short-lasting stabilization may have been considered pseudoprogressors despite the lack of a timely prolonged benefit from ICIs (in the OAK study, patients treated beyond progression received a median of only three cycles of atezolizumab after progression).

Since the early 2000s, the RECIST[19] have been widely used to assess the benefit of anticancer drugs such as chemotherapy and targeted agents: however, their value and clinical applicability have been questioned in the immunotherapy era. In fact, atypical radiological patterns of response (pseudoprogression) or progression (hyperprogression[18,20,21]) occasionally occur upon treatment with ICIs and cannot be properly detected by RECIST. Therefore, immune-related response criteria (irRC) were developed in 2009[1] to provide a more rigorous characterization of the unconventional patterns of response to immunotherapy. The key differences from RECIST were the reintroduction of bidimensional measurements (the sum of products of the two largest perpendicular diameters), the inclusion of new lesions (usually classified as progression according to RECIST version 1.1) in the total tumor burden, and the requirement of confirmation of progression on consecutive scans at least 4 weeks apart.[1] Subsequently, a simplified version of irRC (immune-related RECIST [irRECIST]) was proposed. The irRECIST guidelines used the longest diameter measurements as in RECIST and demonstrated high concordance when compared with bidimensional irRC.[22] Finally, the immune RECIST (iRECIST) were recently developed to standardize response assessment among trials with ICIs.[23] The major change brought by iRECIST was the introduction of immune-unconfirmed progression, which consent to continue treatment at the first progression according to RECIST,

and immune-confirmed progression if progression is confirmed at the next assessment. Unlike in the irRECIST, new lesions are evaluated apart from target lesions and are not added to the total tumor burden.

Immune-related criteria are currently needed to address the full spectrum of immunotherapy activity in evaluation trials. However, beyond dedicated trials, the article by Fujimoto et al.[9] raises questions about the real utility of irRC, irRECIST, and iRECIST to assess responses resulting from use of ICIs in patients with NSCLC in daily practice. In fact, although these criteria make it possible to properly identify pseudoprogression, the low rate of this phenomenon (1%–5%) makes their clinical utility questionable, especially because pseudoprogression is currently a retrospective diagnosis with a lack of associated biomarkers. Moreover, hyperprogression, which is an acceleration of tumor growth upon immune checkpoint blockade,[20,21] seems to be much more frequent than pseudoprogression in NSCLC. Hyperprogression has been recently described in 14% of patients with NSCLC, and it correlates with extremely poor survival compared with that with conventional progression (3.4 months versus 6.2 months [$p = 0.003$]).[18] The fact that hyperprogression drives toward early death (mainly in the first 6 weeks of treatment) not only prompts discussion of an anticipated radiological evaluation at initiation of PD-1/PD-L1 inhibitor therapy but also raises questions regarding the 4 weeks of continuation of treatment beyond progression to follow modified RECIST rules. In fact, in patients with hyperprogression, following the immune-modified RECIST recommendations may delay an early switch to another potentially efficient therapy.

Although the study by Fujimoto et al.[9] is the first exploring the associations between pseudoprogression and patients' clinical characteristics, biomarkers of pseudoprogression are currently lacking. In their study, PD-L1 status was available for only three of 14 patients with pseudoprogression; in addition, no data are reported on blood cell counts, such as derived neutrophil-to-lymphocyte ratio, which has been shown to negatively influence survival of NSCLC treated with PD-1/PD-L1 inhibitors.[24] Of note, patients with relatively high immune suppression in the periphery (i.e., a high derived neutrophil-to-lymphocyte ratio) or in the tumor microenvironment may have a slower antitumor immune response and delayed shrinkage after initial tumor growth, thus being classified as patients with pseudoprogression. In this regard, the tumor microenvironment and the circulating immune cell populations could share common features between patients with pseudoprogression and patients with hyperprogression. Notably, the initial tumor growth in patients with pseudoprogression may sometimes mimic hyperprogression. In this regard, pseudoprogression was retrospectively identified in 10% of patients with NSCLC presenting with a hyperprogressive accelerated tumor growth kinetic pattern during treatment with anti–PD-1/PD-L1 agents.[18] Although the biological bases of pseudoprogression and hyperprogression have not yet been elucidated, it is possible that both these phenomena are characterized by a high immune suppression status that constantly increases upon anti–PD-1/PD-L1 blockade in hyperprogression and is slowly reprogrammed to improve anticancer immunity in patients with pseudoprogression.

In conclusion, pseudoprogression is a rare event that is reported in 2% to 8% of patients with advanced NSCLC treated with anti–PD-1/PD-L1 agents, and it might not justify an extensive use of a confirmatory CT scan outside of clinical trials, as recommended by iRECIST. As long as no reliable biomarkers of efficacy or progression are available, careful evaluation of patients' disease-related symptoms, performance status, and clinical conditions should always be put in perspective along with the results of radiological evaluation to guide physicians' decisions case by case.

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