Letter to the Editor

Dear Sir,

The recent article by Michels and colleagues (2016;4:47-51) highlighted some important considerations regarding the problem of pseudo-progression among cancer patients receiving immunotherapy, the need for immune-related response criteria, and the question of the most appropriate surrogate endpoints to use in clinical trials. To add to these points, while it is indeed correct that pseudo-progression (i.e. a transient increase in tumour size and/or the development of new lesions) is a phenomenon that is typical of immunotherapy, it should be noted that this has been observed more frequently with ipilimumab than with the more recently approved anti-PD-1/PD-L1 agents (e.g. nivolumab, pembrolizumab). Indeed, concerns over pseudo-progression were initially raised in relation to the use of ipilimumab, which is essentially a one-shot single-cycle treatment that is associated with a delayed onset of action. This absence of an immediate effect may be a factor in the lack of improvement seen in surrogate endpoints, such as overall response rate (ORR) and progression-free survival (PFS) with ipilimumab, despite a beneficial effect on overall survival (OS). However, the anti-PD-1 treatments appear to have a faster onset than ipilimumab and so pseudo-progression may be less of a concern with these treatments [1, 2]. Moreover, the seeming discrepancy between surrogate endpoints and OS seen with ipilimumab is less evident. Patients receiving anti-PD-1 therapy should continue treatment while waiting for a subsequent confirmation assessment. Most patients with pseudo-progression can be identified through a further scan after 4 weeks. As noted by Michels et al., immune-related response criteria (irRC) are based on the assessment of total tumoral mass rather than single lesions as is the case with the RECIST criteria. The irRC should be considered together with RECIST criteria in order to prevent premature cessation of anti-PD-1 treatment.

Pseudo-progression also appears to be more evident in melanoma than other tumour types, with around 7-12% of melanoma patients having a clinical response after an initial diagnosis of progressive disease according to RECIST criteria, compared to less than 6% in some solid tumors [3, 4].

Another comment is that the use of surrogate endpoints is more important with regard to the evaluation of long-term benefit from new drugs than problems related to pseudo-progression. Clinical trials need to incorporate endpoints that are accurate as well as efficient to ensure that new agents become available for all patients without unnecessary delays. OS may be the gold standard but it can be years before a trial can provide meaningful OS data, especially if survival is significantly prolonged. PFS has been shown to be a strong surrogate for OS and also has the benefit of not being confounded by post-progression therapy. However, the use of median PFS might underestimate the clinical value of a drug (e.g. if a drug induces long-term responses in a proportion of patients but has no effect at all in a similar proportion). Because of this, landmark PFS analysis at prespecified time points might be a more useful measure [5].

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CANCER BREAKING NEWS 2017;5(1):43-44
DOI: 10.19156/cbn.2017.0040

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