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### **Title**

Anti-PD-1 antibody treatment for melanoma.

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## Anti-PD-1 antibody treatment for melanoma

Beaver and colleagues<sup>1</sup> reported on the rate of radiographic response after documented disease progression by studying a pooled analysis of individual patient data provided to the US Food and Drug Administration in support of the approval of anti-programmed death receptor-1 (PD-1) therapies for patients with advanced melanoma. Defining this rate is of high importance when interpreting clinical trials of a combination of anti-PD-1 antibodies with another agent in the population of patients who did not respond to prior anti-PD-1 therapy. 95 (4%) of 2624 patients had an objective response beyond an initial progression defined by the Response Evaluation Criteria in Solid Tumors (RECIST). Because the overall population of the study included patients who responded to therapy, the authors focused on the 500 patients who initially qualified as having disease progression, were continued on the same treatment after progression, and had follow-up imaging assessments. By doing this, the authors report a 19% (95 of 500) rate of response after initial progression with continuing anti-PD-1 therapy. Notably, the tumour regression plot of baseline

target lesions for those patients who were treated after initial progression included at least 49 patients who had more than 30% decrease in tumour size at the time that they were declared to have progressive disease by RECIST, most frequently because of the detection of a new tumour site.<sup>1</sup> These patients were already showing some evidence of response. We would argue that the more appropriate denominator to derive this rate of response beyond initial progression would include the 1361 patients who had initial progression, which would then result in a rate of 7% of response after progression. This is similar to the rate of delayed responses after initial progression that was analysed prospectively by Hodi and colleagues.<sup>2</sup> Of the 655 patients enrolled in the phase 1 trial<sup>3</sup> of pembrolizumab for patients with melanoma, 327 were followed by imaging scans for 28 weeks. 24 (7%) of these 327 patients had a response after progression. Because there were 401 patients who did not initially respond to therapy in this same clinical trial, the result would be a 6% rate of delayed response among patients without an initial response. Therefore, we believe that single-arm trials in the patient population that progressed despite anti-PD-1 treatment should aim at ruling out a null hypothesis of 6–7% patients

achieving a late response by continued anti-PD-1 therapy, and that it would be ill-advised to design randomised trials with a control group in which patients would be kept on the anti-PD-1 therapy alone, hoping for the increased response rate initially suggested to be in the range of 19%.

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- 1 Beaver JA, Hazarika M, Mulkey F, et al. Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. *Lancet Oncol* 2018; **19**: 229–39.
- 2 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. *J Clin Oncol* 2016; **34**: 1510–17.
- 3 Ribas A, Hamid O, Daud A, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. *JAMA* 2016; **315**: 1600–09.