Safety, Clinical Activity, and Biological Correlates of Response in Patients with Metastatic Melanoma: Results from a Phase I Trial of Atezolizumab—Letter

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Hamid and colleagues report results from a phase I trial of atezolizumab in patients with melanoma (1). The article includes some correlates of response to atezolizumab; however, there is no analysis of the relationship of dose and response. Given that the average steady-state serum trough concentrations at the labeled doses of atezolizumab are 182–226 μg/mL (2), well in excess of Genentech's established target trough concentration of 4–6 μg/mL (3), it is likely that lower dosages and/or less frequent dosing are equally efficacious at a markedly lower cost (4). In addition, lower dosages of PD-1 pathway inhibitors may also reduce the duration and/or severity of immune-related adverse events (5).

Hamid and colleagues suggest that efficacy is reduced at dosages less than 1 mg/kg every 3 weeks, as they excluded such patients from the statistical analyses. This implies that all doses of ≥1 mg/kg every 3 weeks are equally efficacious, well below the current FDA-approved dosing regimens of 840 mg every 2 weeks, 1,200 mg every 3 weeks, or 1,680 mg every 4 weeks. We encourage Hamid and colleagues to provide any data that can refute our hypothesis that a dose as low as 1 mg/kg every 3 weeks is as efficacious as higher doses. As atezolizumab has linear pharmacokinetics, the average steady-state concentration at 1 mg/kg (approximately 80 mg) every 3 weeks would be projected to be 13 μg/mL (one-fifteenth of the average concentration at the labeled dose)–a concentration more than twice Genentech's target (3). It is also plausible that the optimal dose is dependent on one or more of the tissue biomarkers identified by the authors, although there may not be sufficient patients treated at the lowest effective doses to conduct such an analysis.

Disclosure of Potential Conflicts of Interest

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