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

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The assertion of Goldstein and colleagues that lower or less frequent atezolizumab dosing may be therapeutically effective is based on mean steady-state drug concentration data. However, a general consideration in determining the recommended dose is to ensure adequate exposure (trough concentration [C_{trough}] >6 μg/mL) for the majority of patients, including those who may achieve lower than the mean therapeutic exposure with a given dose (1).

Pertinent to this, a dose-escalation study, PCD4989g, wherein atezolizumab was dosed at 0.03 to 20 mg/kg or given as a fixed dose of 1,200 mg administered every 3 weeks, showed that although atezolizumab pharmacokinetics were linear above 1 mg/kg, faster clearance was observed at doses <1 mg/kg (2). Population pharmacokinetic analysis revealed that several factors, including baseline body weight, albumin, tumor burden, and sex contributed to interpatient exposure variability (2). In addition, target-mediated disposition (TMDD) and/or the presence of antidrug antibodies (ADA) contributed to subtherapeutic exposure at lower dosing levels. However, a dose of 15 mg/kg provided adequate exposure in a majority of patients, regardless of baseline characteristics, ADA status, and TMDD.

Thus, even though antitumor activity was observed with atezolizumab doses as low as 1 mg/kg, the above factors suggest that doses <15 mg/kg can result in subtherapeutic C_{trough} in a subpopulation of patients with fast clearance. It is important to note that the projected C_{trough} of 13 μg/mL for a 1 mg/kg atezolizumab dose is only a mean value. The approved dosing schedule of 1,200 mg atezolizumab every three weeks as well as the other approved regimens of 840 mg every two weeks and 1,680 mg every four weeks, all of which are equivalent to 15 mg/kg every three weeks, consider the totality of data to minimize under-dosing of patients (3).

Regarding safety, the maximum tolerated dose for atezolizumab was not achieved at 20 mg/kg, which is higher than the approved dose of 1,200 mg every three weeks. In addition, exposure–safety analyses of the phase III IMvigor211 and OAK studies showed no exposure–safety relationship with adverse events of special interest or grade 3–5 adverse events (3); hence, the evidence does not suggest that a lower atezolizumab dose would improve safety.

Accordingly, the current atezolizumab dosing regimen minimizes the effects of baseline characteristics associated with reduced exposure and fast clearance from TMDD and/or ADA development, thereby ensuring efficacious and safe drug levels for the majority of patients.

Disclosure of Potential Conflicts of Interest

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