Chemoimmunotherapy for stage IV non-small-cell lung cancer

Authors' reply

We appreciate Dipesh Uprety's thoughtful comments. Liver metastasis, considered a poor prognostic factor, has been used for stratification in trials of first-line atezolizumab plus chemotherapy in non-small-cell lung cancer. In IMpower150,[1,2] a significant overall survival benefit was shown in participants receiving atezolizumab plus bevacizumab plus carboplatin and paclitaxel compared with those receiving bevacizumab plus carboplatin and paclitaxel both in the entire intention-to-treat population (hazard ratio [HR] 0·76 [95% CI 0·63–0·93]) and in the subset of the intention-to-treat population with wild-type *EGFR* and *ALK* (HR 0·78 [0·64–0·96]).[1,2] Notably, the overall survival benefit conferred by atezolizumab plus bevacizumab plus carboplatin and paclitaxel appeared to be further enhanced in the liver metastasis subgroup (HR 0·52 [0·33–0·82]).[2] Survival improvement following bevacizumab plus chemotherapy versus chemotherapy alone in patients with non-small-cell lung cancer with liver metastasis was also shown in the E4599 study.[3] However, although results from IMpower130 showed a survival advantage with atezolizumab plus carboplatin and nab-paclitaxel in the intention-to-treat population and most clinical subgroups, this benefit was not observed in patients with liver metastases. Furthermore, interim analysis from IMpower150[2] comparing the atezolizumab plus carboplatin and paclitaxel group with the bevacizumab plus carboplatin and paclitaxel group also did not suggest a survival improvement in this patient population. Together, these data support the hypothesis that adding the combination of atezolizumab and bevacizumab to chemotherapy could enhance overall survival in patients with liver metastases at baseline, possibly because of bevacizumab-mediated effects on the tumour microenvironment and angiogenesis factors. Genomic alterations, including concurrent mutations in *STK11* and *KEAP1*, as potential prognostic or predictive biomarkers, are currently being assessed in atezolizumab lung cancer trials.

In IMpower130, responses and progression-free survival were evaluated using standard Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria. Although different response evaluation criteria, including the immune-related response criteria (irRC), immune-related (ir)RECIST, and immune-modified RECIST (imRECIST),[4] have been developed to capture response patterns specific to immune checkpoint inhibitors, these criteria are considered exploratory and further evaluation and validation are needed. To ensure consistent design and data collection across immunotherapy trials, the RECIST Working Group proposed new guidelines for immunotherapy RECIST (iRECIST) in 2017.[5] Response evaluation per iRECIST could be incorporated into the study designs of future immunotherapy trials.

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