Background Enhancement of antitumor immunity through inhibition of the checkpoint PD-1 receptor has been effective in the treatment of many malignancies. AMG 404 is a monoclonal antibody (mAb) targeting PD-1. This phase 1, open-label, multicenter first-in-human study (NCT03853109) will evaluate the safety, tolerability, pharmacokinetics, and efficacy of AMG 404 monotherapy in adult patients with advanced solid tumors.

Methods The primary study endpoint is dose-limiting toxicity (DLT) and safety; key secondary endpoints include pharmacokinetic parameters, objective response rate (assessed Q8W), duration of response, and progression-free survival. Key inclusion criteria include historically or cytologically proven metastatic or locally advanced solid tumors not amenable to curative treatment with surgery or radiation for which standard therapies have been exhausted or not available. Prior anti-PD-(L)1 or other checkpoint inhibitors were not allowed. Five dose-finding cohorts, including 2 expansion cohorts, ranged from 3–20 patients each. AMG 404 was given until disease progression, intolerance, or consent withdrawal.

Results As of the data cutoff date of May 4, 2020, 62 patients received at least 1 dose of AMG 404 and were included in the safety and efficacy analysis sets. Fifty percent were men, 72% had ECOG 1 performance status, median age was 62 years (range: 28–83), and 42% had ≥3 lines of prior anticancer therapy. Median AMG 404 exposure was ~3 months (maximum: ~12 months). No DLTs were observed. Treatment-related adverse events (TRAEs) were reported for 29 patients (47%): those reported for ≥2 patients were fatigue (n=7); hypothyroidism (n=6); increased blood thyroid stimulating hormone and nausea (n=4 each); increased aspartate aminotransferase, decreased appetite, and pyrexia (n=3 each); and increased alanine aminotransferase, arthralgia, diarrhea, and increased weight (n=2 each). AEs leading to withdrawal of AMG 404 were reported for 3 patients (5%): all were serious and considered to be not related to AMG 404. Sixteen (26%) patients died on study; no deaths were considered related to AMG 404. Preliminary pharmacokinetic results were consistent with those of other therapeutic anti-PD-1 mAbs. Three patients had a confirmed partial response (pancreatic cancer, clear cell cancer, and pleomorphic sarcoma); an additional 4 patients had one scan with a partial response and are pending a confirmatory scan (clear cell renal carcinoma, undifferentiated nasopharyngeal carcinoma, sarcomatoid carcinoma of unknown primary, and colon cancer).

Conclusions AMG 404 is tolerable at the tested doses with no DLTs reported. All observed TRAEs are consistent with other anti-PD-1 therapies. Encouraging anti-tumor activity has been observed in heavily pretreated patients. The study is continuing enrollment into additional cohorts.

Trial Registration NCT03853109

Ethics Approval The study was approved by the Ethics Board of each institution involved in this study and can be produced upon request.