

AVELUMAB + BINIMETINIB IN METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA (MPDAC): DOSE-ESCALATION RESULTS FROM THE PHASE 1B/2 JAVELIN PARP MEKI TRIAL

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Background Preclinical studies of avelumab (anti-PD-L1) + binimetinib (MEK inhibitor [MEKi]) showed encouraging anti-tumor activity. We report results from the phase 1b JAVELIN PARP MEKi trial (NCT03637491) evaluating avelumab + binimetinib in patients with mPDAC.

Methods Eligible patients had mPDAC and disease progression during or following 1–2 prior lines for advanced or metastatic disease. Patients received avelumab 800 mg intravenously every 2 weeks and binimetinib 30 or 45 mg orally twice daily. The primary endpoint for phase 1b was dose-limiting toxicity (DLT). Secondary endpoints included safety, confirmed objective response per investigator (RECIST 1.1), pharmacokinetics, immunogenicity, and biomarker analyses. PD-L1 expression (SP263 assay) and CD8+ tumor-infiltrating lymphocytes (TILs) in baseline tumor samples were assessed using immunohistochemistry. Molecular alterations were assessed via plasma ctDNA analyses. Blood samples were collected to assess trough concentrations for avelumab, binimetinib, and AR00426032 (binimetinib metabolite) and end-of-infusion concentration for avelumab.

Results 22 patients received avelumab + binimetinib 30 mg (n=10) or 45 mg (n=12); all discontinued treatment. Among 21 DLT-evaluable patients, DLTs occurred in 3/10 (30.0%) in the 30-mg group (mucosal inflammation, dermatitis acneiform, blood creatine phosphokinase increased [n=1 each]) and 5/11 (45.5%) in the 45-mg group (detachment of retinal pigment epithelium, abdominal pain, diarrhea, nausea, vomiting, rash pustular, hypertension, blood creatine phosphokinase increased [n=1 each]). Any-grade treatment-related adverse events (TRAEs) occurred in all 22 patients; grade =3 TRAEs occurred in 8 (80.0%) and 4 (33.3%) in the 30- and 45-mg groups, respectively, most commonly blood creatine phosphokinase increased (n=3 [30.0%], n=2 [16.7%], respectively). No treatment-related deaths occurred. Objective response rates (95% CI) in the 30- and 45-mg groups were 0% (0.0–30.8) and 8.3% (0.2–38.5; 1 partial response), respectively; 1 (10.0%) and 6 (50.0%) had a best overall response of stable disease. Tumor shrinkage was associated with higher baseline PD-L1 expression, higher number of CD8+ TILs, and *MEK1/2*, *PIK3CA*, and *RNF43* alterations, whereas *ERBB4* alterations correlated inversely with tumor size change. Available data indicate that avelumab, binimetinib, and AR00426032 exposures were within range of previous monotherapy studies.

Conclusions This study was terminated before a recommended phase 2 dose was established. In patients with mPDAC who received avelumab + binimetinib, DLTs occurred in both dose groups, although TRAEs were generally consistent with single

agent safety profiles. The 45-mg binimetinib dose had a higher number of patients with stable disease and one confirmed partial response. Biomarker findings provide insights into potential mechanisms of treatment resistance and response.

Trial Registration NCT03637491

Ethics Approval The trial was approved by each site's independent ethics committee.

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