## 589 XEVINAPANT PLUS NIVOLUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS WHO PROGRESSED ON PRIOR ANTI–PD-1/PD-L1 TREATMENT: RESULTS OF A DOSE-OPTIMIZATION, EXPLORATORY PHASE 1B/2 TRIAL

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**Background** Anticancer agents that render cancer cells susceptible to apoptosis and increase antitumor immunity may enhance clinical responses to immune checkpoint inhibitors. In this phase 1b/2 trial, we investigated the antitumor activity and safety of xevinapant, a first-in-class, potent, oral, small-molecule inhibitor of apoptosis proteins inhibitor which restores cancer cell sensitivity to apoptosis, in combination with the anti-PD-1 antibody nivolumab.

**Methods** Eligible patients had histologically confirmed advanced or metastatic solid tumors that progressed on prior anti–PD-1/PD-L1 treatment, including small cell lung cancer (cohort 1), squamous cell carcinoma of the head and neck (cohort 2), gastrointestinal cancers with known microsatellite-high (MSI-H)/mismatch repair deficiency (MMRd) or other DNA-damage response (DDR) abnormalities (cohort 3), or platinum-resistant epithelial ovarian, endometrial, primary peritoneal or cervical cancer (with known MSI-H/MMRd, *BRCA1/2* mutations, or other DDR abnormalities; cohort 4). In the dose-escalation part of the trial (part A), patients received xevinapant 150 or 200 mg/day on days 1-10 and days 15-24 plus nivolumab 240 mg on days 1 and 15 of a 28-day cycle. The primary objective of part A was to determine the recommended phase 2 dose (RP2D). In the phase 2 basket trial (part B), patients received xevinapant plus nivolumab at the RP2D; the primary endpoint was objective response rate (ORR).

**Results** Eleven patients were enrolled in part A; 3 patients received xevinapant 150 mg/day and 8 received 200 mg/day. No dose-limiting toxicities during the observation period (28 days) or grade $\geq$3 treatment-related adverse events (TRAEs) were reported. The RP2D was established as xevinapant 200 mg/day (days 1-10 and 15-24) plus nivolumab 240 mg (days 1 and 15) per 28-day cycle.[1] In part B, 35 patients (n=8 cohorts 1-3, n=11 cohort 4) received xevinapant plus nivolumab at the RP2D. Most patients (60.0%) had stage IV disease and all patients had received prior chemotherapy treatment. At data cutoff (April 6, 2022), the ORR was 2.9%, with 1 partial response (cohort 4; endometrial cancer); 15 patients (42.9%) had stable disease. Thirty-four patients (97.1%) had discontinued treatment; the most common reason was disease progression (26 patients; 74.3%). Median PFS across cohorts was 1.9 months (95% CI, 1.7-2.7); median OS was 11.7 months (95% CI, 6.0-15.9). TRAEs occurred in 30 patients (85.7%); grade $\geq$3 TRAEs in 9 patients (25.7%). No treatment-related deaths were reported.

**Conclusions** Xevinapant plus nivolumab had a tolerable safety profile in patients with heavily pretreated solid tumors but limited clinical activity in this immunotherapy-refractory population.

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**Trial Registration** NCT04122625 (ClinicalTrials.gov)

### REFERENCE

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**Ethics Approval** The trial protocol was approved by the independent ethics committee or institutional review board at each participating center.

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