Preliminary results of a phase II study of alrizomadlin (APG-115), a novel, small-molecule MDM2 inhibitor, in combination with pembrolizumab in patients (pts) with unresectable or metastatic melanoma or advanced solid tumors that have failed immuno-oncologic (I-O) drugs.

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Background: Alrizomadlin (APG-115) restores TP53 function, activating p53-mediated apoptosis in tumor cells with wild-type TP53 and/or MDM2 amplification. Alrizomadlin also functions as a host immunomodulator and hence may restore antitumor activity in pts with cancers failing PD-1/PD-L1 blockade. Methods: This US multicenter trial assessed alrizomadlin combined with pembrolizumab in pts with unresectable/metastatic melanoma or advanced solid tumors that had failed I-O drugs; or pts with malignant peripheral nerve sheath tumor (MPNST), liposarcoma, or ATM mutant solid tumors that had failed any standard therapy. Eligible pts had ECOG performance status of 0-2 and no CNS metastases. The phase II study cohorts included pts with melanoma, NSCLC, solid tumor with ATM mutation, well-differentiated/dedifferentiated liposarcoma, urothelial carcinoma, and MPNST. Alrizomadlin was administered orally at 150 mg once every other day for 2 consecutive weeks with 1 week off and pembrolizumab at 200 mg via IV infusion for 30 minutes on Day 1 of a 21-day cycle. Results: As of December 25, 2020, 84 pts had been treated in 6 cohorts: melanoma (n = 26), NSCLC (n = 23), ATM mutation (n = 9), liposarcoma (n = 14), urothelial (n = 9), and MPNST (n = 3). In the PD-1/PD-L1 inhibitor-failed melanoma cohort, there was 1 confirmed partial response (PR) out of 5 pts with uveal melanoma, 2 PR (1 confirmed and 1 unconfirmed) of 5 pts with mucosal melanoma, and 1 confirmed PR of 11 pts with cutaneous melanoma. ORR in the melanoma cohort was 17.4% (4/23 evaluable pts), and the disease control rate was 60.9% (14/23). In the MPNST cohort, 1 of 3 pts had an unconfirmed ongoing PR. In I-O drug-failed NSCLC (n = 14 evaluable) and urothelial (n = 5 evaluable) cohorts, each reported 1 confirmed PR. Common treatment (alrizomadlin or pembrolizumab)-related adverse events (TRAES) (∼10%) were nausea (63.1%), thrombocytopenia (36.9%), vomiting (33.3%), fatigue (31.0%), decreased appetite (27.4%), diarrhea (21.4%), neutropenia (15.4%), and anemia (11.9%). Grade ≥ 3 TRAES (∼5%) included thrombocytopenia (20.2%), neutropenia (14.2%), and anemia (8.3%). Eleven pts discontinued treatment due to AEs: 5 were treatment related, including 2 grade 4 thrombocytopenia, and 1 each of grade 2 vomiting, grade 2 fatigue, and grade 2 posterior reversible encephalopathy syndrome (PRES). Three treatment-related SAEs were PRES, pyrexia, and asthenia. Conclusions: Alrizomadlin combined with pembrolizumab is well tolerated and may restore antitumor effects in pts with cancer resistant to or intolerant of I-O drugs, as suggested by preliminary antitumor activities in multiple tumor types. Internal study identifiers: APG-115-US-002; Keynote MK-3475-B66. Clinical trial information: NCT03611868. Research Sponsor: Ascentage Pharma Group Corp Ltd (Hong Kong).