479 AGEN1181, AN FC-ENHANCED ANTI-CTLA-4 ANTIBODY, ALONE AND IN COMBINATION WITH BALSTILIMAB (ANTI-PD-1) IN PATIENTS WITH ADVANCED SOLID TUMORS: INITIAL PHASE I RESULTS

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Background AGEN1181 is a novel anti-CTLA-4 antibody with enhanced FcγR-dependent functionality, engineered to bind high and low binding alleles of FcγRIIIA, promoting superior T cell priming, memory responses, and depletion of intratumoral T regulatory cells. Further, AGEN1181 avoids complement recruitment, predictive of better tolerability. Here we report initial safety and efficacy findings from a phase I/Ib study of AGEN1181 as monotherapy and in combination with balstilimab (BAL; anti-PD-1).

Methods Eligible patients (pts) had advanced solid tumors refractory to standard therapies. AGEN1181 was dosed Q3W (0.1–3 mg/kg) or Q6W (1–2 mg/kg) as monotherapy, or Q6W (0.1–2 mg/kg) in combination with BAL Q2W (3 mg/kg).

Results As of July 16th 2021, 102 pts received AGEN1181 (43 monotherapy, 59 combination). Median age, 63 years (29–83); 50.5% with ≥3 prior lines of therapy. MTD not yet reached with AGEN1181 dosing up to 3 mg/kg Q3W as monotherapy and 2 mg/kg in combination with BAL. The most common treatment-related adverse events (TRAEs) of any grade were fatigue (34.3%), diarrhea (32.4%), and nausea (19.6%) with grade ≥3 events in 21.6% (diarrhea/colitis, 11.8%, fatigue, 2.9%). Notably, no immune-related hypophysitis or pneumonitis has been observed. Discontinuation from AGEN1181 due to TRAEs occurred in 15% of pts. Grade 5 TRAEs occurred in two pts (colitis [chronic], intestinal perforation). The disease control rate in evaluable pts (completed ≥1 on-treatment scan) defined as best overall response of CR, PR, or SD ≥6 weeks was 48.1% for AGEN1181 monotherapy ≥1 mg/kg (1 CR, 3 PR, 9 SD) and 70% for combination (3 PR, 6 unconfirmed PR [uPR], 19 SD). Monotherapy responders include individual pts with MSS endometrial cancer (CR), PD-1-relapsed/refractory cervical cancer (PR), PD-1-relapsed/refractory melanoma (PR), and pancreatic cancer (PR). Enrollment is continuing in several disease expansion cohorts with combination therapy. For MSS CRC, 2 PR, 2 uPR, and 7 SD have been seen in 17 evaluable ≥1 mg/kg patients to date. In the ovarian cohort (n=6), 2 PRs and 3 SD are noted. Additional combination responders include one PR and uPR in MSS endometrial cancer, two uPRs in visceral angiosarcoma (uPRs) and one uPR in PD-1-relapsed/refractory NSCLC (uPR); the majority of the responses are recent and ongoing.

Conclusions AGEN1181 alone and in combination with BAL demonstrates favorable tolerability and compelling clinical activity, notably in poorly immunogenic tumor types and PD-1-refractory pts. These results underscore the significant potential of AGEN1181 to expand benefit of anti-CTLA-4 therapy to a broader patient population.

Trial Registration NCT03860272

Ethics Approval The study obtained ethics approval at each participating center (UT Health Sciences Center at San Antonio, University of Colorado Cancer Center, St John's Cancer Institute, and HonorHealth under WIRB Study number 1256391; USC Norris Comprehensive Cancer Center, Beth Israel Deaconess Medical Center, and MD Anderson Cancer Center, approval numbers HS19-00277, 19–132, and 140346, respectively). All patients provided written informed consent in accordance with federal, local, and institutional guidelines.

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