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 histologically or cytologically proven solid tumors to evade the anticancer immune response. ALX148 is a Fc region designed to safely enhance anticancer therapeutics. 1

Results: A total of 92 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 aspar- tate aminotransferase, decreased appetite, and pyrexia (n=3 each); and increased alanine aminotransferase, arthralgia, diarrhea, and increased weight (n=2 each). AEIs 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 consid- ered 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 carci- noma 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 continu- ing 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.

Trial Registration: NCT04291079

ALX148, a CD47 BLOCKER, IN COMBINATION WITH STANDARD CHEMOTHERAPY AND ANTIBODY REGIMENS IN PATIENTS WITH GASTRIC/ GASTROESOPHAGEAL JUNCTION (GC) CANCER AND HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

Background: CD47 is a myeloid checkpoint up-regulated in tumors to evade the anticancer immune response. ALX148 is a high affinity CD47-blocking fusion protein with an inactive Fc region designed to safely enhance anticancer therapeutics. 2

Methods: ALX148 in combination with standard chemotherapy and antibody regimens was evaluated in patients (pts) with advanced HER2-positive GC or HNSCC. Pts with previously treated advanced HER2-positive GC or untreated advanced HNSCC received ALX148 (A) 10 mg/kg QW or 15 mg/kg QW in combination with trastuzumab (T) + ramucirumab (ram) + paclitaxel (pac) as 2nd or later- line treatment or pembrolizumab (P) + 5FU + platinum (cis- platin or carboplatin) as 1st line therapy, respectively. The pri- mary endpoint was dose limiting toxicity (DLT). Tumor response, pharmacokinetic (PK), and pharmacodynamic (PD) markers were assessed in all pts. Preliminary data from enrolling cohorts, and follow-up data from pts with GC
administered A+T, and with HNSCC administered A+P are also reported as of 30June2020.

Results Fifty-five pts enrolled into this portion of the study. Twelve patients with ≥2L GC received A+T+ram+pac and were evaluated for safety. No DLTs were reported, and the ALX148 maximum administered dose was 15 mg/kg QW. Out of the 9 pts who experienced any adverse event, 7 pts reported treatment-related adverse events (TRAES). The most common TRAEs were low grade diarrhea, fatigue, pruritus and rash (each n=2,179%). Nine of the 12 patients were response-evaluable and reported a 66% ORR with 6PR and 3SD (including one ongoing near PR, |29.9%|). Three patients with 1L HNSCC were administered A+P+5FU+platinum. No DLTs were reported and accrual to 15 mg/kg QW continues. Three pts experienced any AE, none were treatment-related. Of 3 evaluable patients with HNSCC, 2PR and 1SD were reported. Initial ALX148 combination PK and CD47 target occupancy are similar to that of single agent administration. Response duration and survival follow-up of 19 pts with HER2-positive GC administered A+T (2nd or later-line; 21% ORR) and of 10 pts with checkpoint inhibitor naïve HNSCC administered A+P (2nd or later-line; 40% ORR) will be reported. Results of all cohorts will be updated at time of presentation.

Conclusions Initial data suggests the myeloid checkpoint inhibitor, ALX148, is well tolerated in combination with the above antitumor antibodies, T-cell checkpoint inhibitor, and cytotoxic chemotherapy regimens with early anticancer signals in GC and HNSCC that compare favorably with historic controls. No MTD has been reached in any combination to date and accrual to chemotherapy combination regimens is ongoing.

Trial Registration ClinicalTrials.gov identifier NCT03013218

Ethics Approval The study was approved by all participating institutions’ Ethics and/or Review Boards

REFERENCES


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CDX1140–01, A PHASE 1 DOSE-ESCALATION/EXPANSION STUDY OF CDX-1140 ALONE (PART 1) AND IN COMBINATION WITH CDX-301 (PART 2) OR PEMBROLIZUMAB (PART 3)

1 Rachel Sarbenn, 2 Ralph Hauke, 3 Natasha Gabrail, 4 Mark O’Hara, 5 Nina Bhardwaj, 6 Rodolfo Bordoni, 7 Michael Gordon, 8 Danny Khalil, 9 Maen Abdelrahim, 10 Thomas Marron, 11 Thomas Hawthorne, 12 Lawrence Thomas, 13 Tracey Rawls, 14 Mark Rogalski, 15 Diego Alvarado, 16 Laura Vitale, 17 Tito Kele, 18 Michael Yellin. Providence Cancer Center, Portland, OR, USA; 1 Nebraska Cancer Center, Omaha, NE, USA; 2 Gabriel Cancer Center, Canton, OH, USA; 3 Abramson Cancer Center at University of Pennsylvania, Philadelphia, PA, USA; 4 Mount Sinai Hospital, New York, NY, USA; 5 Northside Hospital, Marietta, GA, USA; 6 HonorHealth, Scottsdale, AZ, USA; 7 Memorial Sloan Kettering Cancer Center, New York, NY, USA; 8 Houston Methodist Hospital, Houston, TX, USA; 9 Mount Sinai Hospital, New York, NY, USA; 10 Cellax Therapeutics, Hampton, NJ, USA; 11 Cellax Therapeutics, Hampton, NJ, USA

Background CDX-1140 is an agonist anti-CD40 mAb selected to optimize systemic exposure and hence tumor microenvironment (TME) ingress. CDX-1140 activity may be enhanced by combining with CDX-301 (recombinant Flt3L), a dendritic cell growth factor, or with pembrolizumab, an anti-PD-1 mAb.

Methods Patients with advanced solid or hematologic (Part 1 only) tumors are enrolled. Part 1 dose-escalation results have been presented (SITC 2019). In Part 2, CDX-1140 dose-escalation (0.09–1.5 mg/kg q4w) is in combination with CDX-301 (75 mcg/kg sc QD x 5 for 2 cycles). In Part 3, CDX-1140 dose-escalation (0.72–1.5 mg/kg q3w) is in combination with pembrolizumab 200 mg q3w. Part 1 and 2 expansion cohorts are dosed at the CDX-1140 MTD, 1.5 mg/kg q4w. Part 3 expansion cohorts are planned. Peripheral blood and tumor biomarkers analysis are ongoing.

Results 92 patients have been treated (Part 1 n=57, Part 2 n=31, Part 3 n=4). Part 1 expansion cohorts in SCCHN (n=7) and RCC (n=5) are fully enrolled. Part 2 dose-escalation completed to the highest CDX-1140 dose and a SCCHN expansion cohort is ongoing. Part 3 dose-escalation recently initiated. Safety data is available for 23 and 10 patients at the MTD in Part 1 and 2, respectively. In general, the safety profiles were similar, with arthralgia (52% vs. 50%), pyrexia (44% vs 50%), fatigue (30% vs. 50%), chills (39% vs. 40%), vomiting (30% vs. 20%), nausea (26% vs 40%), myalgia (22% vs. 30%), increased ALT (22% vs. 20%), and increased AST (22% vs 30%) being the most common drug related AEs at the MTD. Most AEs were low grade. Across all cohorts, cytokine release syndrome (CRS) (G2 n=4, G3 n=2) occurred in 6 (Part 1 n=2; Part 2 n=4) and pneumonitis (G3) occurred in 5 (Part 1 n=4; Part 2 n=1) patients. Immune activation in the TME consistent with CD40 agonism and increases serum inflammatory cytokines were observed. Evidence of anti-tumor activity/clinical benefit include SD (n=13), tumor cavitation (n=2) and a uPR in one ongoing durable complete metabolic response.

Conclusions The CDX-1140 MTD dose of 1.5 mg/kg, a dose level expected to provide good systemic exposure and TME penetration, is generally well tolerated alone and with CDX-301. Transaminitis and CRS have generally been low grade and infrequent. A cohort combining CDX-1140 with chemotherapy will be initiated in patients with previously untreated metastatic pancreatic adenocarcinoma.

Trial Registration NCT03329950

Ethics Approval The study was approved by the following: Providence St. Joseph Health IRB, approval number MOD2020001128; WIRB, approval number 1188814 (Hauke, Gabrail, Bordoni & Gordon); University of Pennsylvania IRB, approval number UPPC 18917; Mount Sinai School of Medicine IRB, approval number 18-00202; Memorial Sloan Kettering Cancer Center IRB, approval number 18-225A; Houston Methodist IRB, approval number MOD00000836

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