Abstract 9534: Phase 1b/2, Open Label, Multicenter, Study of the Combination of SD-1 and Pembrolizumab in Patients with Advanced Melanoma Who Are Naive to Anti-PD-L1/PD-1 Therapy (SYNERGY-001/KEYNOTE-184, NCT02521870)

M. Milimer1, G.V. Long1, C.J. Homes1, A. Amiri2, C. Lao2, R.M. Conry3, J. Hunt4, G. Daniels5, M. Almubarak6, M. Shaheen7, T. Medina8, M. Barve9, S. Bistis10, S. Abdi11, M. Chisarmore12, B. Xing13, C. Guiducos14, E. Gamelin15, R. Janssen16, A. Ribas17


Background: Pembrolizumab (Keytruda) is an anti-PD-1 monoclonal antibody that is approved by the FDA for the treatment of patients with melanoma and non-small cell lung cancer. The addition of pembrolizumab to programmed death-ligand 1 (PD-L1) blockade has significantly improved outcomes in advanced melanoma, yet durable responses are only observed in a subset of patients. The efficacy and safety of the combination of pembrolizumab with SD-1 (pembrolizumab) is being evaluated in the SYNERGY-001 study (NCT02521870). Here we report the results of the phase 1b portion of this study.

Methods: A phase 1b, open-label, multicenter trial enrolled patients with a variety of advanced solid tumors, including melanoma, for whom pembrolizumab was indicated. pembrolizumab was administered by I.V. (150 mg) every 2 weeks for 4 cycles followed by every 4 weeks for up to 2 years. SD-1 (pembrolizumab) was administered by I.V. (0.1–10 mg/100 mg) on study days 1, 8, 15, and 22. Patients were enrolled in a 3-of-3 rule design, where 3 patients were treated simultaneously in each cohort. A total of 37 patients were treated in 3 cohorts (0/1/2/3 mg or 0/1/2 mg SD-1 dose compared with 8 mg pembrolizumab). Dose escalation was guided by the number of patients with at least 1 grade 3 or 4 adverse event (AE) in the previous cohort. Patients who did not achieve a clinical benefit at the dose escalation threshold proceeded to the next cohort. Patients with progressive disease (PD) were allowed to continue pembrolizumab given a positive response to pembrolizumab alone. Dose escalation was guided by the number of patients with at least 1 grade 3 or 4 AE in the previous cohort. Patients who did not achieve a clinical benefit at the dose escalation threshold proceeded to the next cohort. Patients with progressive disease (PD) were allowed to continue pembrolizumab given a positive response to pembrolizumab alone.

Results: Patients had a median age of 62 (range: 22–85), and 62% were male. The majority of patients had metastatic disease (65%). Common PD-L1 expression status was PD-L1+ (n = 21), PD-L1− (n = 15), and unknown (n = 1). The patients had a median Karnofsky performance status of 80 (range: 20–90), median ECOG PS of 0 (range: 0–2), and median number of prior systemic treatments of 3 (range: 1–12). Baseline LDH, Median (Q1, Q3) = 195 (181, 246) and 16% had a BRAF V600E mutation.

Efficacy: Of the 37 patients treated, 28 (76%) had SD-1 responsive lesions. Best response was as follows: CR n = 1 (3), PR n = 18 (48), SD n = 7 (19), PD n = 1 (3). Median duration of response (DOR) was 7.2 months (95% CI: 1.0, 20.0). Among the 28 SD-1 responsive lesions, 7 (25%) had a confirmed partial response (CPR), 9 (32%) had a confirmed SD (CSD), and 1 (4%) had a confirmed PD (CPD). Best overall response rate (ORR) was 101% (95% CI: 90%, 100%) for any SD-1 responsive lesion and 36% (95% CI: 20%, 54%) for any pembrolizumab responsive lesion (ITT). Median follow-up was 11.1 months (range: 1.8–21.1). Safety: Treatment-related adverse events (TRAEs) ≥ grade 3 occurred in 8 (22%) patients. 2 (5%) had grade 3/4 pneumonitis, both of which were radiographic worsening of pre-existing disease at baseline. 8 (22%) had grade 3/4 toxicities typical of pembrolizumab, including 1 (3%) Grade 3/4 hypophysitis. 1 (3%) had grade 3/4 infections with bacterial meningitis. 1 (3%) had grade 3/4 autoimmune hepatitis.

Conclusion: The combination of pembrolizumab with SD-1 has shown high clinical activity and tolerability in multiple disease types, including melanoma. Future studies will explore the role of pembrolizumab with or without SD-1 in the treatment of advanced solid tumors.