DOSE ESCALATION OF NEXT GENERATION ANTI-CTLA-4 ANTIBODY ONC-392 IN COMBINATION WITH FIXED DOSE OF PEMBROLIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Combination of CTLA-4 and PD-1/PD-L1 targeting antibodies are effective cancer immunotherapy with great potential, but the high risk of severe toxicity limits clinical development. Our preclinical studies suggest that acid pH-sensitive anti-CTLA-4 antibodies that preserve CTLA-4 recycling by avoiding lysosomal degradation are more effective for immunotherapy while largely devoid of immunotherapy-related adverse events (irAE) when used in combination with anti-PD-1 antibodies. We previously showed the recommended phase II dose (RP2D) of ONC-392 monotherapy is 10mg/kg IV Q3W.1 In the current study, we evaluated the safety and tolerability of ONC-392 in combination with pembrolizumab.

Methods ONC-392-001 (NCT04140526 ) Part B is a dose finding study of ONC 392 at 3 mg/kg (cohort 1) or 6 mg/kg (cohort 2) in combination with a fixed dose of pembrolizumab 200 mg, IV, Q3W. We enrolled patients with advanced/metastatic solid tumors whose disease had progressed on standard of care (SOC) therapies and pembrolizumab was approved as SOC. The primary endpoints are safety, tolerability and RP2D of ONC-392 in combination with pembrolizumab (RP2D-C).

Results Cohort 1 enrolled 7 patients and cohort 2 enrolled 6 patients, including 4 NSCLC, 5 melanoma, 1 each with cervical, TNBC, HCC and CuSCC. Patient characteristics are listed in table 1. Eleven patients had prior anti-PD-1/PD-L1 and 5 melanoma patients had prior ipilimumab. The mean cycles of treatment are 5.7 cycles (1-13) in 5.2 months and 4.5 cycles (1-9) in 4.1 months in cohort 1 and 2, respectively. None of the 13 pts experienced dose limiting toxicity (DLT) in the DLT period. Treatment related AEs (TRAEs) were observed in 11 (85%) patients without Grade 4 or 5 TRAEs. Grade 3 TRAEs were observed in 5 pts (38.5%) (3/7 in cohort 1 and 2/6 in cohort 2); infusion reaction (2) and immune-mediated colitis (3). Three patients (23%) had Gr 3 irAEs in the form of immune colitis or colitis. The RP2D-C is determined to be 6.0 mg/kg ONC-392+ 200 mg of pembrolizumab Q3W. Two confirmed PR (TNBC and cervical cancer, ORR=29%, DQR=6 months) and 4 SD in cohort 1, and 3 SD and 1 PD in cohort 2 were observed (figure 1).

Conclusions ONC-392 combination with pembrolizumab is safe and clinically active. The rate of irAE is low relative to drugs of the same class. These results support the feasibility to significantly increase drug exposure for full immunotherapeutic potential of anti-CTLA-4 and anti-PD-1 combination therapy.

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