PHARMACOKINETICS OF FIRST AND REPEATED DOSING OF NON-IRAE-INDUCING ANTI-CTLA-4 MONOCLONAL ANTIBODY ONC-392 IN ADVANCED CANCER PATIENTS

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Background ONC-392 preserves CTLA-4 recycling and thereby maintains its physiological immune tolerance check-point function while allowing more efficient and selective elimination of tumor-infiltrating regulatory T cells. The safety data in the first-in-human trial showed that ONC-392 is safe and well tolerated with no observed immunotherapy-related adverse events (irAE). Serum samples were used to determine pharmacokinetic parameters of ONC-392 to establish systemic drug exposure.

Methods Samples from the first and third dosing cycles were collected at predose and 0.5, 6, 24, 48, 192, 360, and 504 hours postdose. For other dosing cycles, predose and 0.5 hour postdose samples were collected. Serum ONC-392 concentrations were measured by ELISA and the PK parameters were analyzed under noncompartmental condition using linear trapezoidal method.

Results Systemic exposure of ONC-392 is positively correlated to dosing concentration and number of doses. Mean C_{max} and AUC 0–504hr values increase proportionately to dosing concentrations from 0.1mg/kg to 10mg/kg. Dose ratio in cycle 1 is 1:3:30:100. The mean cycle 1 C_{max} and AUC 0–504hr ratios are 1:3.34:31.32:106.28 and 1:3.13:28.46:100.63 respectively. The C_{max} in patients receiving one or more doses of ONC-392 at 3mg/kg is 89±16µg/mL. The C_{max} in patients receiving one or more doses of ONC-392 at 10mg/kg is 259±55µg/mL. Inclusive of all dosing concentrations (0.1, 0.3, 1, 3, 10mg/kg) and cycles, T_{max} is between 1.5–6 hours with one outlier observed at 24-hour postdose. The t_{1/2} range from 201 to 478 hours (8 - 20 days). The cycle 1 mean of t_{1/2} for 0.1, 0.3, 3, 10mg/kg dosing concentrations are 411.02, 359.25, 246.22, 355.01 hours respectively. A direct comparison between first and third cycle in the 3mg/kg dosing group confirms ONC-392 accumulation in repeated dosing. The trough levels (C_{min}) in patients receiving one or multiple doses of ONC-392 at 3mg/kg and 10mg/kg are between 12–51µg/mL and 49–71µg/mL respectively. Lastly, inclusive of all dosing concentrations (0.1, 0.3, 1, 3, 10mg/kg) and cycles, MRT range from 307.91–655.04 hours, V_z range from 0.0305–0.0726 mg/(µg/mL), and Cl range from 0.000052–0.00019 mg/(µg/mL)/h.

Conclusions Intravenous infusion of ONC-392 provide adequate and dose-dependent exposure over extended period. Overall exposure is comparable or higher than those reported by others using different anti-CTLA-4 antibodies. The apparent lack of irAE in ONC-392 recipients despite the high exposure indicates intrinsic safety and tolerability of ONC-392.

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