



# Pharmacokinetics of First and Repeated Dosing of 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 checkpoint 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.

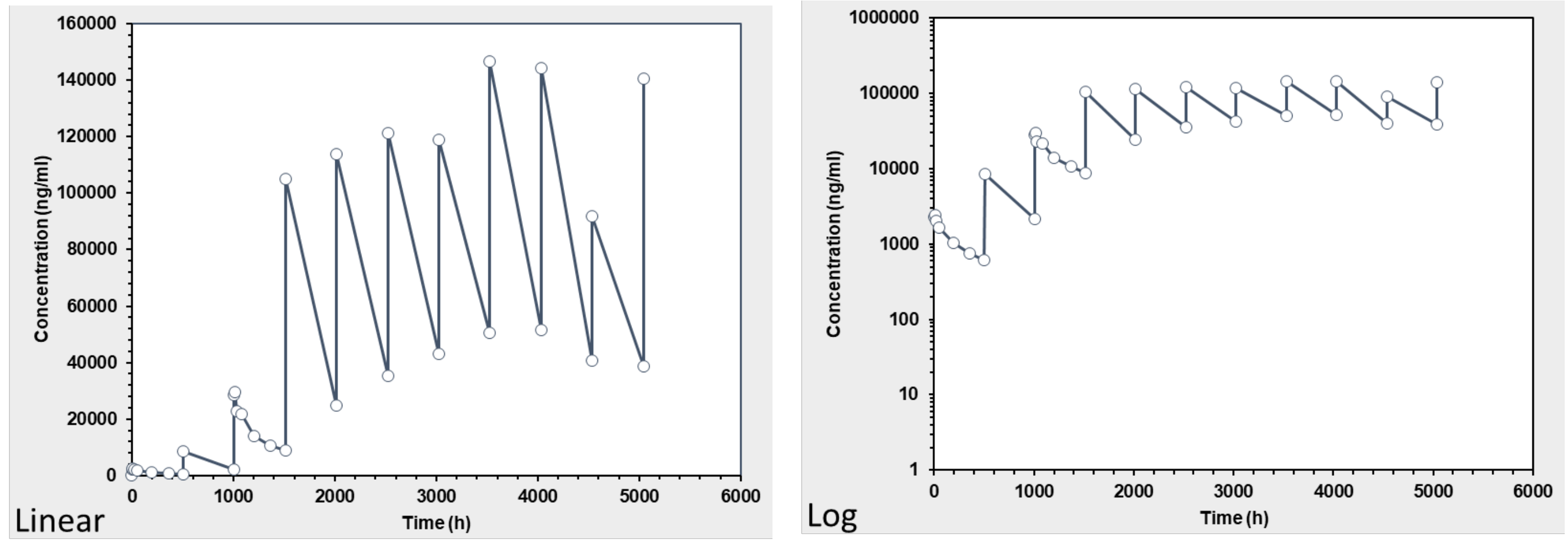
**Method:** Samples from the first and third dosing cycles were collected at predose and 0.5, 6, 24, 48, 192, 360, and 504 hours postdose. For other dosing cycles, predose and 0.5 hour postdose samples were collected. Serum ONC-392 concentrations were measured by ELISA and the PK parameters were analyzed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

**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. Remarkably, ONC-392 was well tolerated among patients who has received repeated dosing of 3.0 mg/kg and 10.0 mg/kg of ONC-392.

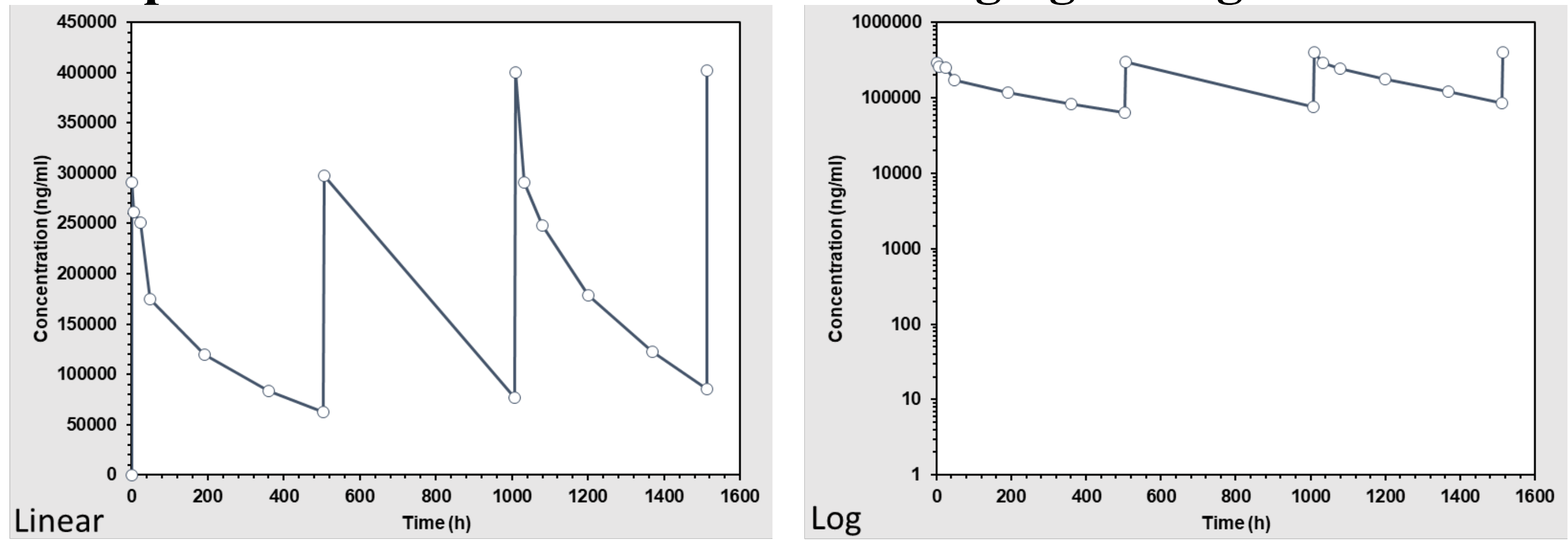
## Results:

|                             | Weeks | 3    | 6          | 9    | 12  | 24        | 36        |
|-----------------------------|-------|------|------------|------|-----|-----------|-----------|
| #1: Ovarian cancer          | 0.1   | 0.3  | 1.0<br>SD  | 3.0  | 3.0 | 3.0<br>SD | 3.0<br>SD |
| #2: Cervical cancer         | 0.3   | 1.0  | 3.0<br>SD  | 3.0  | 3.0 |           |           |
| #3: Gastroesophageal cancer | 3.0   | 3.0  | 3.0<br>SD  | 3.0  | PD  |           |           |
| #4: Lung cancer             | 3.0   | 3.0  | 3.0<br>SD  | 3.0  | 3.0 | 3.0<br>SD | 3.0       |
| #5: Lung cancer             | 10.0  | 10.0 | 10.0<br>SD | 10.0 | PD  |           |           |
| #6: Lung cancer             | 10.0  | 10.0 | 10.0<br>SD | 10.0 | CR  | CR*       |           |
| #7: Ovarian cancer          | 10.0  | 10.0 | 10.0<br>SD | 10.0 |     |           |           |
| #8: Ovarian cancer          | 10.0  | 10.0 | 10.0<br>SD | 10.0 | PD  |           |           |
| #9: Lung cancer             | 10.0  | 10.0 | 10.0<br>SD | 10.0 |     |           |           |
| #10: Ovarian cancer         | 10.0  | 10.0 | 10.0<br>SD | 10.0 | CR* |           |           |

Pt #1 Dose escalated from 0.3mg/kg to 3mg/kg



Pt #7 PK profile with four treatments of 10mg/kg dosing



## Summary of Plasma ONC-392 PK Parameters by Dosing:

| Parameter Statistic          | ONC-392 0.1mg/kg Cycle 1 | ONC-392 0.3mg/kg Cycle 1 | ONC-392 1mg/kg Cycle 3 | ONC-392 3mg/kg Cycle 1 | ONC-392 3mg/kg Cycle 3 | ONC-392 10mg/kg Cycle 1 | ONC-392 10mg/kg Cycle 3 |
|------------------------------|--------------------------|--------------------------|------------------------|------------------------|------------------------|-------------------------|-------------------------|
| <b>Cmax (µg/ml)</b>          |                          |                          |                        |                        |                        |                         |                         |
| n                            | 1                        | 1                        | 1                      | 2                      | 3                      | 6                       | 3                       |
| Mean (SD)                    | 2.44                     | 8.17                     | 29.47                  | 76.43 (1.34)           | 96.56 (11.54)          | 283.47 (43.99)          | 352.34 (72.68)          |
| CV%                          | N/A                      | N/A                      | N/A                    | 1.76                   | 11.95                  | 15.52                   | 20.63                   |
| Median                       | N/A                      | N/A                      | N/A                    | 76.43                  | 91.92                  | 295.35                  | 387.50                  |
| Min, Max                     | N/A                      | N/A                      | N/A                    | 75.48, 77.383          | 88.06, 109.70          | 195.90, 316.70          | 268.80, 400.80          |
| <b>Cmin (Trough) (µg/ml)</b> |                          |                          |                        |                        |                        |                         |                         |
| n                            | 1                        | 2                        | 2                      |                        |                        | 6                       | 3                       |
| Mean (SD)                    | 0.61                     | 2.15 (0.04)              | 8.59 (0.34)            | N/A                    | N/A                    | 50.82 (13.65)           | 81.85 (20.98)           |
| CV%                          | N/A                      | 1.87                     | 3.96                   |                        |                        | 26.86                   | 25.63                   |
| Median                       | N/A                      | 2.15                     | 8.59                   |                        |                        | 44.86                   | 85.29                   |
| Min, Max                     | N/A                      | 2.12, 2.17               | 8.35, 8.83             |                        |                        | 34.20, 67.24            | 50.37, 100.90           |
| <b>Tmax (hr)</b>             |                          |                          |                        |                        |                        |                         |                         |
| n                            | 1                        | 1                        | 1                      | 2                      | 3                      | 6                       | 3                       |
| Mean (SD)                    | 6                        | 1.5                      | 6                      | 1.5 (0)                | 9 (12.99)              | 1.5 (0)                 | 1.5 (0)                 |
| CV%                          | N/A                      | N/A                      | N/A                    | 0                      | 144.34                 | 0                       | 0                       |
| Median                       | N/A                      | N/A                      | N/A                    | 1.5                    | 1.5                    | 1.5                     | 1.5                     |
| Min, Max                     | N/A                      | N/A                      | N/A                    | N/A                    | 1.5, 24                | N/A                     | N/A                     |
| <b>t½ (hr)</b>               |                          |                          |                        |                        |                        |                         |                         |
| n                            | 1                        | 1                        | 1                      | 2                      | 3                      | 6                       | 3                       |
| Mean (SD)                    | 411.02                   | 359.25                   | 477.86                 | 246.22 (64.56)         | 411.42 (41.80)         | 315.80 (72)             | 264.40 (58.65)          |
| CV%                          | N/A                      | N/A                      | N/A                    | 26.22                  | 10.16                  | 22.8                    | 22.18                   |
| Median                       | N/A                      | N/A                      | N/A                    | 246.22                 | 401.83                 | 289.93                  | 288.16                  |
| Min, Max                     | N/A                      | N/A                      | N/A                    | 200.57, 291.87         | 375.24, 457.18         | 206.19, 407.62          | 197.59, 307.44          |
| <b>AUC 0-504hr (µg/ml*h)</b> |                          |                          |                        |                        |                        |                         |                         |
| n                            | 1                        | 1                        | 1                      | 2                      | 3                      | 6                       | 3                       |
| Mean (SD)                    | 539.94                   | 1,690.07                 | 7,179.13               | 15,364.41 (4,336.71)   | 24,010.60 (7,509.85)   | 51,564.58 (9,435.34)    | 84,465.58 (17,219.69)   |
| CV%                          | N/A                      | N/A                      | N/A                    | 28.23                  | 31.28                  | 18.3                    | 20.39                   |
| Median                       | N/A                      | N/A                      | N/A                    | 15,364.41              | 20,052.66              | 55,918.98               | 85,572.71               |
| Min, Max                     | N/A                      | N/A                      | N/A                    | 12,297.89, 18,430.92   | 19,307.57, 32,671.55   | 40,950.06, 62,207.15    | 66,719.04, 101,105.00   |
| <b>AUC0-inf (µg/ml*h)</b>    |                          |                          |                        |                        |                        |                         |                         |
| n                            | 1                        | 1                        | 1                      | 2                      | 3                      | 6                       | 3                       |
| Mean (SD)                    | 899.35                   | 2,789.88                 | 13,269.35              | 20,936.27 (7,199.48)   | 41,290.75 (13,709.35)  | 75,689.33 (17,581.04)   | 119,816.83 (27,306.71)  |
| CV%                          | N/A                      | N/A                      | N/A                    | 34.39                  | 33.2                   | 23.13                   | 22.8                    |
| Median                       | N/A                      | N/A                      | N/A                    | 20,936.27              | 34,339.28              | 69,883.76               | 122,190.14              |
| Min, Max                     | N/A                      | N/A                      | N/A                    | 15,845.47, 26,027.07   | 32,449.67, 57,083.31   | 5,285.27, 101,749.43    | 91,400.92, 145,859.42   |