Poster #243

A phase 1 study of fixed-dose regimens of serplulimab, an anti-PD-1 antibody, in patients with advanced solid tumors

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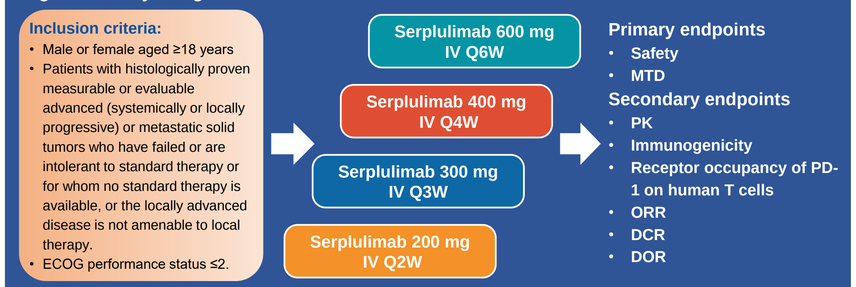
Background

- Serplulimab is a recombinant humanized IgG4 monoclonal antibody targeting programmed death 1 (PD-1). Compared with nivolumab and pembrolizumab, serplulimab recognizes PD-1 in a unique manner and has higher affinity to human PD-1[1,2]. Serplulimab is also more potent at blocking programmed death ligand 1 signaling.
- A two-cohort phase 1 study was conducted to evaluate the safety of serplulimab monotherapy in patients with advanced solid tumors (NCT03468751). Findings from the dose-finding cohort has been previously reported[3].
- Here we present results from the dose expansion cohort, in which we evaluated the safety, pharmacokinetics (PK), pharmacodynamics, and preliminary efficacy of fixed-dose regimens of serplulimab in patients with advanced solid tumors.

Methods

- This multicenter phase 1 study enrolled patients with locally advanced or metastatic solid tumors who have failed or are intolerant to standard therapy or for whom no standard therapy was available.
- In the dose expansion cohort, patients received intravenous serplulimab at 200 mg every 2 weeks (Q2W), 300 mg every 3 weeks (Q3W), 400 mg every 4 weeks (Q4W), or 600 mg every 6 weeks (Q6W; **Figure 1**).
- Tumor imaging by computed tomography or magnetic resonance imaging was scheduled at baseline, every 6 weeks (for the 300 mg Q3W and 600 Q6W groups) or 8 weeks (for the 200 mg Q2W and 400 mg Q4W groups) for 24 weeks from the first dose, and every 12 weeks thereafter. Tumor response status was assessed according to Response Evaluation Criteria in Solid Tumors v1.1.

Figure 1. Study design



DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; PD-1, programmed death-1; PK, pharmacokinetic(s); Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks.

Conclusions

Fixed-dose regimens of serplulimab showed favorable safety, PK, and pharmacodynamic characteristics and preliminary anti-tumor activity, supporting its further investigation.

Results

- As of January 5, 2024 (database lock date), 37 patients received at least one dose of serplulimab at 200 mg Q2W (n = 9), 300 mg Q3W (n = 9), 400 mg Q4W (n = 10), or 600 mg Q6W (n = 9; **Table 1**).
- All patients were Asian. 26 (70.3%) patients were male. The median age was 60.0 years (range, 33–88).
- Overall, 24 patients (64.9%) had metastatic disease. All patients had prior systemic anticancer treatment, including 4 (10.8%) with prior immunotherapy; 19 patients (51.4%) had ≥ 3 prior lines of therapy.
- All 37 patients received at least one administration of the study treatment and were included in safety, PK, and pharmacodynamics analyses.

Table 1. Patient demographics and baseline characteristics

	200 mg (n = 9)	300 mg (n = 9)	400 mg (n = 10)	600 mg (n = 9)
Median age (range), years	61.0 (34–78)	60.0 (33–73)	59.5 (37–73)	61.0 (39–88)
Male, n (%)	6 (66.7)	8 (88.9)	7 (70.0)	5 (55.6)
Disease status				
Locally advanced	3 (33.3)	2 (22.2)	5 (50.0)	3 (33.3)
Metastatic	6 (66.7)	7 (77.8)	5 (50.0)	6 (66.7)
Clinical stage				
I	0	1 (11.1)	0	0
IV	9 (100)	8 (88.9)	10 (100)	8 (88.9)
Not available	0	0	0	1 (11.1)
Primary tumor location (top 3)				
Head and neck	0	2 (22.2)	5 (50.0)	2 (22.2)
Esophagus	2 (22.2)	3 (33.3)	1 (10.0)	0
Colorectum	2 (22.2)	0	1 (10.0)	1 (11.1)
Prior systemic anticancer treatment				
Chemotherapy	9 (100)	9 (100)	10 (100)	9 (100)
Immunotherapy	1 (11.1)	0	2 (20.0)	1 (11.1)
Prior line(s) of systemic anticancer treatment				
1	9 (100)	9 (100)	9 (90.0)	9 (100)
2	8 (88.9)	9 (100)	7 (70.0)	5 (55.6)
≥3	4 (44.4)	7 (77.8)	6 (60.0)	2 (22.2)

Safety

- The median duration of exposure to serplulimab was 14.0 weeks (range, 1–130).
- No dose-limiting toxicity was reported. Maximum tolerated dose has not been determined.
- Overall, 34 (91.9%) patients experienced at least one treatment-emergent adverse event (TEAE), including 14 patients (37.8%) who experienced at least one grade ≥3 TEAE (**Table 2**).
- Nineteen (51.4%) patients experienced at least one serplulimab-related TEAE, including 7 (18.9%) who experienced at least one grade ≥3 serplulimab-related TEAE.
- Immune-related adverse events were reported in 11 patients (29.7%; grade ≥3, 4/37, 10.8%) and infusion-related reactions in 2 patients (5.4%).
- The most common (occurring in ≥4 patients in the overall population) TEAEs are shown in **Table 3**.

Table 2. Summary of adverse events

	200 mg (n = 9)	300 mg (n = 9)	400 mg (n = 10)	600 mg (n = 9)
Any TEAE	9 (100)	8 (88.9)	9 (90.0)	8 (88.9)
Grade ≥3	3 (33.3)	4 (44.4)	5 (50.0)	2 (22.2)
Serious	5 (55.6)	1 (11.1)	4 (40.0)	2 (22.2)
Leading to tx discontinuation	1 (11.1)	1 (11.1)	2 (20.0)	2 (22.2)
Leading to death	2 (22.2)	0	0	1 (11.1)
Any serplulimab-related TEAE	6 (66.7)	5 (55.6)	5 (50.0)	3 (33.3)
Grade ≥3	3 (33.3)	1 (11.1)	2 (20.0)	1 (11.1)
Serious	2 (22.2)	1 (11.1)	2 (20.0)	1 (11.1)
irAE	2 (22.2)	4 (44.4)	3 (30.0)	2 (22.2)
IRR	0	0	0	2 (22.2)

Table 3. Most common TEAEs[a]

	200 mg (n = 9)	300 mg (n = 9)	400 mg (n = 10)	600 mg (n = 9)
Pyrexia	4 (44.4)	4 (44.4)	0	0
Decreased appetite	3 (33.3)	2 (22.2)	2 (20.0)	1 (11.1)
Pruritus	3 (33.3)	2 (22.2)	1 (10.0)	2 (22.2)
Diarrhea	3 (33.3)	0	2 (20.0)	1 (11.1)
Pneumonia	2 (22.2)	2 (22.2)	1 (10.0)	1 (11.1)
Constipation	2 (22.2)	2 (22.2)	0	1 (11.1)
Fatigue	2 (22.2)	1 (11.1)	1 (10.0)	1 (11.1)
Blood creatinine increased	1 (11.1)	3 (33.3)	0	1 (11.1)
Dyspnea	3 (33.3)	1 (11.1)	0	0
Insomnia	2 (22.2)	2 (22.2)	0	0
Cough	2 (22.2)	1 (11.1)	1 (10.0)	0
Rhinorrhea	2 (22.2)	1 (11.1)	1 (10.0)	0
Hypokalemia	2 (22.2)	0	1 (10.0)	1 (11.1)
Rash	1 (11.1)	3 (33.3)	0	0

[a] *Occurring in ≥4 patients in the overall population.*

irAE, immune-related adverse event; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event; tx, treatment.

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Pharmacokinetics, immunogenicity, and pharmacodynamics

- Following multiple serplulimab administrations, the geometric mean $C_{max,ss}$ was 107.6–282.2 μg/mL across dose levels; and the geometric mean AUC_{ss} was 23310 h*μg/mL–94740 h*μg/mL.
- The geometric mean $t_{½,ss}$ was from 341.1–751.3 h, and the geometric mean CL_{ss} was 0.006–0.009 L/h.
- Treatment-emergent anti-drug antibody (ADA) was detected in 7 (18.9%) patients. No difference in safety or PK was noted between ADA-positive and -negative patients.
- Profiles of PD-1 receptor occupancy in circulating CD3+ T cells and interleukin-2 stimulation ratio were similar across dose groups, suggesting dose-independent functional blockade.

Efficacy

- Of the 37 patients, 2 discontinued from the study prior to post-baseline tumor response evaluations and without experiencing death or disease progression. The remaining 35 patients were included in efficacy analysis.
- Four patients from the 300 mg Q3W group and 2 from the 400 mg Q4W group achieved partial response, resulting in confirmed objective response rates of 44.4% and 22.2% in the respective groups (**Table 4**).
- The duration of study treatment and best overall response of each patient is illustrated in **Figure 2**.
- Among the responders in the 300 mg Q3W and 400 mg Q4W groups, the median duration of response (DOR) was not reached (95% confidence interval, 2.7–NE) and not evaluable (NE; NE–NE; **Table 4**), respectively. The 12-month DOR rates were 75.0% (12.8%–96.1%) and 50.0% (NE–NE).
- The median progression-free survival was 1.7 months (0.6–NE), 5.6 months (1.2–NE), 3.0 months (1.7–5.5), and 7.4 months (1.2–NE) in the 200 mg Q2W, 300 mg Q3W, 400 mg Q4W, and 600 mg Q6W groups, respectively (**Table 4**).

Table 4. Efficacy according to assessments by investigator per RECIST v1.1

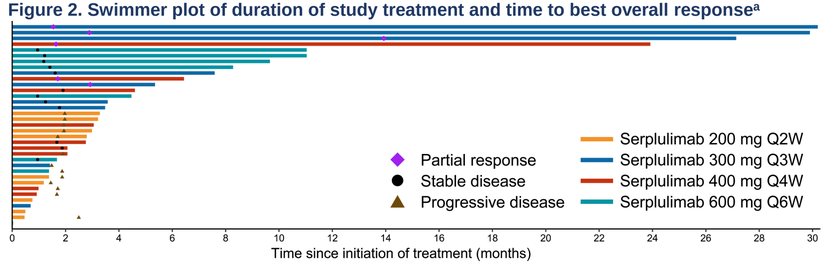
	200 mg (n = 9)	300 mg (n = 9)	400 mg (n = 9)	600 mg (n = 8)
Best overall response[a]				
CR, n (%)	0	0	0	0
PR, n (%)	0	4 (44.4)	2 (22.2)	0
SD, n (%)	0	3 (33.3)	3 (33.3)	6 (75.0)
PD, n (%)	7 (77.8)	1 (11.1)	4 (44.4)	1 (12.5)
NE, n (%)	0	0	0	0
ORR, n (%)[a]	0	4 (44.4)	2 (22.2)	0
DCR, n (%)[a]	0	7 (77.8)	5 (55.6)	6 (75.0)
No. of responders[a]	0	4	2	0
Median DOR, months (95% CI)[a,b]	NA	NR (2.7–NE)	NE (NE–NE)	NA
12-month DOR rate, % (95% CI)[a]	NA	75.0 (12.8–96.1)	50.0 (NE–NE)	NA
Median PFS, months (95% CI)	1.7 (0.6–NE)	5.6 (1.2–NE)	3.0 (1.7–5.5)	7.4 (1.2–NE)
6-month PFS rate, % (95% CI)	0 (NE–NE)	44.4 (13.6–71.9)	11.1 (0.6–38.8)	50.0 (15.2–77.5)

[a] *Tumor responses were confirmed.*

[b] *Median DOR were analyzed only for dose groups in which at least 3 patients achieved objective response.*

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; NA, not applicable; NE, not evaluable; No., number; NR, not reached; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Figure 2. Swimmer plot of duration of study treatment and time to best overall response[a]



[a] *Four patients died without post-baseline tumor response assessments.*

Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; Q6W, every 6 weeks.

References

1. PLOS ONE. 2021;16(12):e0257972
2. MAbs. 2024;16(1):2419838.
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