The Oncologist®

Clinical Trial Results

First-in-Human Phase I Study of Envafolimab, a Novel Subcutaneous Single-Domain Anti-PD-L1 Antibody, in Patients with Advanced Solid Tumors

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Key Words. Envafolimab • Anti-PD-L1 • Advanced solid tumors

Trial Information

- **ClinicalTrials.gov Identifier**: NCT02827968
- **Sponsor:** 3D Medicines Co., Ltd
- **Principal Investigator:** Wael Harb
- **IRB Approved:** Yes

Lessons Learned

- Subcutaneous injection was an effective route of administration for envafolimab with a favorable pharmacokinetic profile in patients with previously treated advanced solid tumors.
- Subcutaneous envafolimab was well tolerated and had durable antitumor activity at a wide range of doses and schedules.
- Envafolimab has the potential to be a more convenient option than currently approved intravenous PD-1/PD-L1 inhibitors.

Abstract

Background. Envafolimab is a novel fusion of a humanized single-domain PD-L1 antibody and human IgG1 Fc fragment formulated for subcutaneous injection. This study explored the safety and feasibility of subcutaneous administration of envafolimab as an alternative to intravenous administration of PD-1/PD-L1 inhibitors in the treatment of advanced, refractory solid tumors.

Methods. This was a first-in-human, open-label phase I trial. In a dose-escalation phase, patients received subcutaneous envafolimab 0.01–10 mg/kg once weekly following a modified 3+3 design. In a dose-exploration phase, patients received subcutaneous envafolimab 300 mg once every 4 weeks.

Results. Twenty-eight patients were enrolled (dose escalation $n = 18$, dose exploration $n = 10$, median age 66 years; 71% male; ECOG performance score = 0 [21%] or 1 [79%]). No dose-limiting toxicities or injection-site reactions were reported. Envafolimab demonstrated dose-proportional increases in area under the time-concentration curve and maximum plasma concentration. Median time to maximum plasma concentration was 4–7 days. In the dose-exploration phase, terminal half-life was 14 days after dose 1 in cycle 1 and 23 days at steady state. Three patients experienced a confirmed partial response.

Conclusion. Subcutaneous envafolimab had a favorable safety and pharmacokinetic profile, with promising preliminary antitumor activity in patients with advanced solid tumors. ***The Oncologist*** 2021;26:e1514–e1525

Discussion

Envafolimab is a novel recombinant protein of a humanized single-domain anti-PD-L1 antibody fused with a human IgG1 Fc fragment formulated for subcutaneous (SC) injection. This was a first-in-human phase I study to evaluate the safety and feasibility of SC administration of envafolimab as an alternative to intravenous administration of PD-1/PD-L1 inhibitors in the treatment of advanced, refractory solid tumors.

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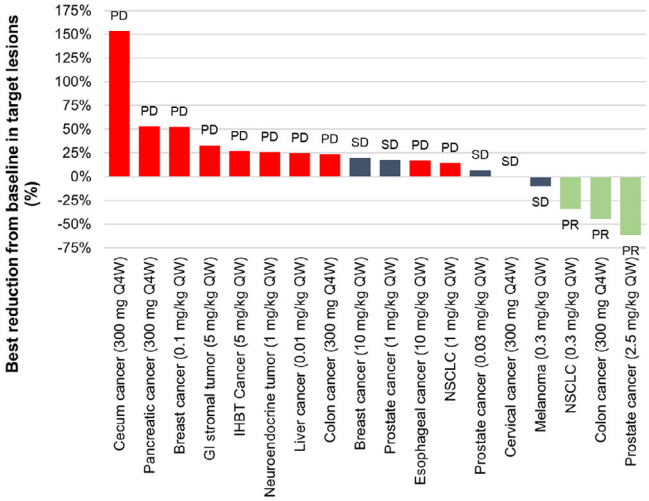

Figure 1. Waterfall plot of tumor reduction from baseline during the dose-escalation and dose-exploration phases ($n = 18$). Abbreviations: GI, gastrointestinal; IHBT, intrahepatic biliary tract; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; Q4W, once every 4 weeks; QW, once weekly; SD, stable disease.

Twenty-eight patients were included. The most common treatment-emergent adverse events (reported in >3 patients) were fatigue (29%), nausea (18%), diarrhea (14%), and hypothyroidism (14%). No grade ≥4 study drug–related treatment-emergent adverse events, dose-limiting toxicities, or injection-site reactions were reported. Antidrug antibodies were detected in 12 (43%) patients, although they were transient in most and did not appear to affect pharmacokinetic exposure to envafolimab.

Objective tumor responses were observed in three patients across several dose cohorts and at a dose as low as 0.3 mg/kg once weekly (QW; Fig. 1). These responses were durable (24.1+ to 59.9+ weeks), and two of the patients still had partial responses assessed at the time of data cutoff (November 25, 2019).

Following a single SC administration in the dose-escalation phase, the maximum plasma concentration (C_{max}) and area under the curve (AUC) increased linearly over the dose range of 0.01 to 10 mg/kg (Fig. 2). At 0.3 mg/kg, two of three patients had a first-dose C_{max} that exceeded 0.5 µg/mL. Median time to reach C_{max} was 4–7 days. Neither first-dose C_{max} nor AUC were significantly affected by injection site. During the dose-exploration phase, in which all patients received envafolimab 300 mg SC once every 4 weeks, the mean C_{max} after the first dose was 14 µg/mL, the AUC up to the last measured concentration (week 4) was 5,850 hours*µg/mL, and the median time to reach C_{max} was 3 days. The first-dose half-life was estimated to be 14 days. At steady state, the mean effective half-life was 23 days.

The results show that SC injection of envafolimab was an effective route of administration, was well tolerated, and had durable antitumor activity at a wide range of doses and schedules in patients with previously treated advanced solid tumors (Table 1; Fig. 1).

Table 1. Simulated pharmacokinetic data for envafolimab dosing regimens: predicted peak and trough concentrations

				Estimated blood concentration of envafolimab		
Dosing regimen	**Dose**	**Measurement**	**Week**	**Geometric mean, mg/L (95% CI)**	**5th percentile, µg/mL**	**10th percentile, µg/mL**
300 mg Q4W	1	Peak	1	11.9 (11.8, 12.0)	4.53	5.78
	1	Trough	4	5.12 (5.07, 5.17)	2.04	2.53
	8	Peak	29	20.4 (20.2, 20.6)	7.34	9.29
	8	Trough	32	9.68 (9.55, 9.81)	3.11	3.98
300 mg Q3W	1	Peak	1	11.9 (11.8, 12.0)	4.53	5.78
	1	Trough	3	6.79 (6.72, 6.86)	2.80	3.47
	8	Peak	22	24.1 (23.8, 24.4)	8.82	11.10
	8	Trough	24	14.2 (14.0, 14.4)	4.86	6.16
400 mg Q4W	1	Peak	1	15.9 (15.7, 16.1)	6.04	7.70
	1	Trough	4	6.83 (6.76, 6.89)	2.72	3.38
	8	Peak	29	27.2 (26.9, 27.5)	9.93	12.40
	8	Trough	32	12.9 (12.7, 13.1)	4.14	5.30
150 mg QW	1	Peak	1	5.97 (5.90, 6.03)	2.28	2.90
	1	Trough	2	5.82 (5.76, 5.87)	2.39	2.97
	8	Peak	8	24.5 (24.2, 24.7)	9.83	12.10
	8	Trough	9	21.9 (21.7, 22.2)	8.86	10.90

Abbreviations: CI, confidence interval; Q3W, once every 3 weeks; Q4W, once every 4 weeks; QW, weekly.

Trial Information	
Disease	Advanced cancer/solid tumor only
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	No designated number of regimens

Type of Study	Phase I, dose escalation + dose exploration
Primary Endpoint	Safety, tolerability
Secondary Endpoints	Maximum tolerated dose, recommended phase II dose, pharmacodynamics, other
Additional Details of Endpoints or Study Design	The study included dose escalation and dose exploration. For the dose escalation, a modified 3+3 design was used, with dose-limiting toxicity (DLT) evaluated up to 28 days after the first dose. Eight dose levels were evaluated. The first three dose levels were assessed in single-patient cohorts. If a grade ≥2 drug-related adverse event (AE) was observed during the DLT period, two additional patients were enrolled and administered the same dose. For the remaining dose levels, a standard 3+3 design was followed. In the dose exploration, patients received envafolimab 300 mg SC once every 4 weeks (Q4W).
Investigator's Analysis	Active and should be pursued further

Drug Information: Dose Escalation	
Envafolimab	
Generic Name	Envafolimab
Company Name	KN035
Drug Type	Antibody
Drug Class	Immune therapy
Dose	0.01, 0.03, 0.1, 0.3, 1, 2.5, 5, and 10 mg/kg
Route	Subcutaneous
Schedule of Administration	In the dose escalation, envafolimab was administered on days 1, 8, 15, and 22 in each 28-day cycle.

Drug Information: Dose Exploration	
Envafolimab	
Generic Name	Envafolimab
Company Name	KN035
Drug Type	Antibody
Drug Class	Immune therapy
Dose	300 mg per flat dose
Route	Subcutaneous
Schedule of Administration	In the dose exploration, patients received envafolimab as a single fixed dose of 300 mg on day 1 in each 28-day cycle.

Patient Characteristics: Dose Escalation	
Number of Patients, Male	13
Number of Patients, Female	5
Stage	III: $n = 1$ IV: $n = 17$
Age	Median (range): 71 (53–79) years
Performance Status: ECOG	0: n = 3 1: n = 15
Cancer Types or Histologic Subtypes	Prostate cancer, 5 Intrahepatic biliary tract cancer, 1 Non-small cell lung cancer, 2 Breast cancer, 2 Cervical cancer, 1 Bladder cancer, 1 Esophageal cancer, 1

	Head and neck cancer, 1 Liver cancer, 1 Melanoma, 1 Neuroendocrine tumor, 1 Gastrointestinal stromal tumor, 1

Patient Characteristics: Dose Exploration	
Number of Patients, Male	7
Number of Patients, Female	3
Stage	IV: $n = 10$
Age	Median (range): 63 (35–77) years
Performance Status: ECOG	0: n = 3 1: n = 7
Cancer Types or Histologic Subtypes	Colorectal cancer, 5 Intrahepatic biliary tract cancer, 2 Prostate cancer, 1 Cervical cancer, 1 Pancreatic cancer, 1

Patient Characteristics: Total	
Number of Patients, Male	20
Number of Patients, Female	8
Stage	III: $n = 1$ IV: $n = 27$
Age	Median (range): 66 (35–79) years
Performance Status: ECOG	0: n = 6 1: n = 22
Cancer Types or Histologic Subtypes	Prostate cancer, 6 Colorectal cancer, 5 Intrahepatic biliary tract cancer, 3 Non-small cell lung cancer, 2 Breast cancer, 2 Cervical cancer, 2 Bladder cancer, 1 Esophageal cancer, 1 Head and neck cancer, 1 Liver cancer, 1 Melanoma, 1 Neuroendocrine tumor, 1 Gastrointestinal stromal tumor, 1 Pancreatic cancer, 1

Secondary Assessment Method: Dose Escalation	
Title	Tumor response
Number of Patients Screened	19
Number of Patients Enrolled	18
Number of Patients Evaluable for Toxicity	18

Number of Patients Evaluated for Efficacy	16
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 2$ (11%)
Response Assessment SD	$n = 5$ (28%)
Response Assessment PD	$n = 9$ (50%)
Response Assessment OTHER	$n = 2$ (11%)
Median Duration of Treatment	10.1 weeks
Outcome Notes	For Response Assessment, "OTHER" denotes not evaluable (efficacy could not be assessed in two patients because they had no postbaseline tumor assessment).

Secondary Assessment Method: Dose Exploration	
Title	Tumor response
Number of Patients Screened	19
Number of Patients Enrolled	10
Number of Patients Evaluable for Toxicity	10
Number of Patients Evaluated for Efficacy	8
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 1$ (10%)
Response Assessment SD	$n = 3$ (30%)
Response Assessment PD	$n = 4$ (40%)
Response Assessment OTHER	$n = 2$ (20%)
Median Duration of Treatment	8.4 weeks
Outcome Notes	For Response Assessment, "OTHER" denotes not evaluable (efficacy could not be assessed in two patients because they had no postbaseline tumor assessment).

Secondary Assessment Method: Total	
Title	Tumor response
Number of Patients Screened	38
Number of Patients Enrolled	28
Number of Patients Evaluable for Toxicity	28
Number of Patients Evaluated for Efficacy	24
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 3$ (11%)
Response Assessment SD	$n = 8$ (29%)
Response Assessment PD	$n = 13$ (46%)
Response Assessment OTHER	$n = 4$ (14%)
Median PFS	2.8 months, 95% CI: 1.8–7.6
Median OS	8.5 months, 95% CI: 3.1–17.4
Median Response Duration	24.9 weeks
Median Duration of Treatment	8.6 weeks

Outcome Notes

For Response Assessment, "OTHER" denotes not evaluable (efficacy could not be assessed in four patients because they had no postbaseline tumor assessment).
The three patients who achieved a PR comprised one patient with non-small cell lung cancer who received 0.3 mg/kg envafolimab QW (response duration 24.9 weeks), one patient with microsatellite instability–high prostate cancer who received 2.5 mg/kg envafolimab QW (response duration 59.9+ weeks), and one patient with microsatellite stable, tumor mutation burden–high (16 mutations/Mb) colon cancer who received 300 mg Q4W (response duration 24.1+ weeks).
At data cutoff (November 25, 2019), 24 of the 28 patients had discontinued treatment. The main reasons for treatment discontinuation were disease progression ($n = 17$) and unacceptable adverse events ($n = 4$). Duration of treatment ranged from 3.9 to 66.1+ weeks.

Adverse Events: Dose Escalation

All Dose Levels, All Cycles

Name	NC/NA	1	2	3	4	5	All grades
Fatigue	61%	22%	17%	0%	0%	0%	39%
Nausea	78%	11%	11%	0%	0%	0%	22%
Alanine aminotransferase increased	83%	6%	0%	11%	0%	0%	17%
Aspartate aminotransferase increased	83%	6%	0%	11%	0%	0%	17%
Diarrhea	83%	11%	6%	0%	0%	0%	17%
Dry mouth	83%	17%	0%	0%	0%	0%	17%
Abdominal pain	89%	0%	0%	11%	0%	0%	11%
Blood alkaline phosphatase increased	89%	0%	0%	11%	0%	0%	11%
Constipation	89%	6%	6%	0%	0%	0%	11%
Decreased appetite	89%	6%	6%	0%	0%	0%	11%
Hypokalemia	89%	11%	0%	0%	0%	0%	11%
Hypomagnesemia	89%	11%	0%	0%	0%	0%	11%
Hypophosphatemia	89%	6%	0%	6%	0%	0%	11%
Hypothyroidism	89%	0%	11%	0%	0%	0%	11%
Lymphopenia	83%	0%	0%	11%	6%	0%	17%
Musculoskeletal chest pain	89%	11%	0%	0%	0%	0%	11%
Musculoskeletal stiffness	89%	11%	0%	0%	0%	0%	11%
Pain in extremity	89%	11%	0%	0%	0%	0%	11%
Rash maculo-papular	89%	11%	0%	0%	0%	0%	11%
Salivary hypersecretion	89%	6%	6%	0%	0%	0%	11%
Skin abrasion	89%	6%	6%	0%	0%	0%	11%
Vomiting	89%	11%	0%	0%	0%	0%	11%

Adverse Events Legend
Adverse events occurring in ≥10% of patients are shown.
There were no DLTs.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events: Dose Escalation

Name	Grade	Attribution
Lung infection	3	Unrelated
Pneumonia	3	Unrelated
Pneumothorax	3	Unrelated
Pneumothorax	3	Unrelated
Compression fracture	3	Unrelated

Pneumonia	3	Unrelated
Gastroenteritis	3	Unrelated
Viral infection	3	Unrelated
Pancreatitis	2	Unrelated
Rectal hemorrhage	3	Unrelated
Deep vein thrombosis	3	Unrelated
Bile duct obstruction	3	Unrelated
Abdominal pain	3	Possible
Aspartate aminotransferase increased	3	Possible
Alanine aminotransferase increased	3	Possible

Serious Adverse Events Legend
The two SAEs of pneumonia and two SAEs of pneumothorax all occurred in the same patient.
The SAEs of viral infection and pancreatitis occurred >30 days after the last dose of study drug.

Adverse Events: Dose Exploration

All Cycles

Name	NC/NA	1	2	3	4	5	All Grades
Dehydration	70%	10%	10%	10%	0%	0%	30%
Enterocolitis infectious	80%	0%	20%	0%	0%	0%	20%
Hypothyroidism	80%	0%	20%	0%	0%	0%	20%
Allergic rhinitis	90%	10%	0%	0%	0%	0%	10%
Back pain	90%	0%	0%	10%	0%	0%	10%
Blepharitis	90%	0%	10%	0%	0%	0%	10%
Cough	90%	10%	0%	0%	0%	0%	10%
Dermatitis acneiform	90%	10%	0%	0%	0%	0%	10%
Diarrhea	90%	0%	0%	10%	0%	0%	10%
Diverticulitis	90%	0%	0%	10%	0%	0%	10%
Dyspnea	90%	0%	0%	0%	0%	10%	10%
Fatigue	90%	10%	0%	0%	0%	0%	10%
Fecaloma	90%	0%	0%	10%	0%	0%	10%
Hypokalemia	90%	0%	10%	0%	0%	0%	10%
Hypomagnesemia	90%	0%	10%	0%	0%	0%	10%
Nausea	90%	0%	10%	0%	0%	0%	10%
Pneumonitis	90%	10%	0%	0%	0%	0%	10%
Rectal tenesmus	90%	0%	10%	0%	0%	0%	10%
Sepsis	90%	0%	0%	0%	10%	0%	10%
Urinary tract infection	90%	0%	10%	0%	0%	0%	10%
Vomiting	90%	0%	10%	0%	0%	0%	10%
Wound	90%	0%	10%	0%	0%	0%	10%

Adverse Events Legend
Adverse events occurring in ≥10% of patients are shown.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events: Dose Exploration

Name	Grade	Attribution
Sepsis	4	Unlikely
Sepsis	3	Unlikely
Sepsis	4	Unlikely
Diverticulitis	3	Unrelated
Fecaloma	3	Unrelated

Back pain	3	Unrelated
Dehydration	3	Unrelated
Urinary tract infection	2	Unrelated
Dyspnea	5	Unrelated

Serious Adverse Events Legend
The three SAEs of sepsis all occurred in the same patient.

Adverse Events: Total

All Dose Levels, All Cycles

Name	NC/NA	1	2	3	4	5	All grades
Fatigue	71%	18%	11%	0%	0%	0%	29%
Nausea	82%	7%	11%	0%	0%	0%	18%
Diarrhea	86%	7%	4%	4%	0%	0%	14%
Hypothyroidism	86%	0%	14%	0%	0%	0%	14%
Alanine aminotransferase increased	89%	4%	0%	7%	0%	0%	11%
Aspartate aminotransferase increased	89%	4%	0%	7%	0%	0%	11%
Dehydration	89%	4%	4%	4%	0%	0%	11%
Dry mouth	89%	11%	0%	0%	0%	0%	11%
Hypokalemia	89%	7%	4%	0%	0%	0%	11%
Hypomagnesemia	89%	7%	4%	0%	0%	0%	11%
Lymphopenia	89%	0%	0%	7%	4%	0%	11%
Vomiting	89%	7%	4%	0%	0%	0%	11%

Adverse Events Legend
Adverse events occurring in ≥10% of patients are shown.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events: Total

Name	Grade	Attribution
Lung infection	3	Unrelated
Pneumonia	3	Unrelated
Pneumothorax	3	Unrelated
Pneumothorax	3	Unrelated
Compression fracture	3	Unrelated
Pneumonia	3	Unrelated
Gastroenteritis	3	Unrelated
Viral infection	3	Unrelated
Pancreatitis	2	Unrelated
Rectal hemorrhage	3	Unrelated
Deep vein thrombosis	3	Unrelated
Bile duct obstruction	3	Unrelated
Abdominal pain	3	Possible
Aspartate aminotransferase increased	3	Possible
Alanine aminotransferase increased	3	Possible
Sepsis	4	Unlikely
Sepsis	3	Unlikely
Sepsis	4	Unlikely
Diverticulitis	3	Unrelated
Fecaloma	3	Unrelated
Back pain	3	Unrelated
Dehydration	3	Unrelated

Urinary tract infection	2	Unrelated
Dyspnea	5	Unrelated

Serious Adverse Events Legend
The two SAEs of pneumonia and two SAEs of pneumothorax all occurred in the same patient.
The SAEs of viral infection and pancreatitis occurred >30 days after the last dose of study drug.
The three SAEs of sepsis all occurred in the same patient.

Pharmacokinetics/Pharmacodynamics: Dose Escalation

Dose level	Dose of drug: envafolimab	No. enrolled	C_{max} (μg/mL) mean (CV)	T_{max} (hours) median (min–max)	$AUC_{0–last}$ (hours*μg/mL) mean (CV)
1	0.01 mg/kg	1	0.370	167	48.0
2	0.03 mg/kg	1	0.095	96.0	7.60
3	0.1 mg/kg	1	0.702	168	81.5
4	0.3 mg/kg	3	0.588 (68%)	97.1 (95.8–144)	75.9 (73%)
5	1 mg/kg	3	2.87 (30%)	97.4 (50.7–168)	367 (32%)
6	2.5 mg/kg	3	10.8 (35%)	96.3 (48.8–168)	1,494 (33%)
7	5 mg/kg	3	19.4 (29%)	121 (97.0–167)	2,330 (54%)
8	10 mg/kg	3	32.9 (37%)	95.9 (95.9–167)	4,483 (43%)

Pharmacokinetics/Pharmacodynamics: Dose Exploration

Dose level	Dose of drug: envafolimab	No. enrolled	C_{max} (μg/mL) mean (CV)	T_{max} (hours) median (min–max)	$AUC_{0–last}$ (hours*μg/mL) mean (CV)	t½ (hours) mean (CV)	Cl F (mL/hour) mean (CV)	V/F (L) mean (CV)
1 (cycle 1, day 1)	300 mg	10	14.0 (32%)	71.9 (47-3-167)	5,850 (39%)	362 (36%)	36.5 (25%)	18.7 (44%)
1 (cycle 5, day 1)	300 mg	3	23.1 (6.3%)	70.6 (46.9-93.5)	10,533 (4.8%)	546 (8.9%)	28.5 (4.6%)	16.7 (20%)

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Currently approved anti-PD-1/PD-L1 antibodies are administered intravenously (IV). The potential benefits of subcutaneous (SC) administration facilitated the discovery and development of envafolimab, a recombinant protein of a humanized single-domain anti-PD-L1 antibody fused with a human IgG1 Fc fragment [1]. In a first-in-human phase I study, the safety, tolerability, pharmacokinetics, and anti-tumor activity of SC envafolimab (200 mg/mL) were evaluated in 28 adults with advanced, refractory solid tumors.

In a dose-escalation phase, no dose-limiting toxicities were reported, the maximum tolerated dose was not reached, and the maximum dose administered was 10 mg/kg once weekly (QW). As of the data cutoff date, there were no infusion-related or injection-site reactions in any treated patient. Treatment-emergent adverse events (TEAEs) reported in >3 patients included fatigue ($n = 8$), nausea ($n = 5$), diarrhea ($n = 4$), and hypothyroidism ($n = 4$). Grade ≥3 TEAEs occurred in 10 of 18 patients in the dose-escalation phase and 4 of 10 in the dose-exploration phase. Fourteen patients overall had TEAEs considered to be drug related, most of which were grade ≤2. The most common of these were expected and previously reported for other PD-1/PD-L1 antibodies in patients with solid tumors [2–4]. Three patients reported grade 3 study drug–related TEAEs, including lymphocytopenia ($n = 1$, 0.1 mg/kg), abdominal pain ($n = 1$, 10 mg/kg), and increased alanine aminotransferase, aspartate aminotransferase, and blood alkaline phosphatase ($n = 2$, 10.0 mg/kg). No grade ≥4 study drug–related TEAEs were reported in either the dose-escalation or dose-exploration phase. A single patient who received 10 mg/kg envafolimab in the dose-escalation phase had three serious TEAEs considered related to the study drug (grade 3 events of abdominal pain, increased alanine aminotransferase, and increased aspartate aminotransferase). These were treated with corticosteroids and resolved with sequelae. Five patients (18%) experienced TEAEs leading to treatment discontinuation. In one patient, these events (increased alanine aminotransferase and aspartate aminotransferase) were considered to be drug related.

Three patients had confirmed partial responses according to RECIST version 1.1 (Fig. 1), of whom two had an ongoing response at data cutoff. Eight patients who received envafolimab had a best overall response of stable disease. The disease control rate was 39.3% (95% confidence interval [CI], 21.5–59.4), and the objective response rate was 10.7% (95% CI,

2.3–28.2), in line with the efficacy of other anti-PD-1/PD-L1 antibodies in previously treated patients with advanced solid tumors [3, 5, 6]. Best reductions in tumor size from baseline are shown in Figure 1. The median progression-free survival was 2.8 months (95% confidence interval, 1.8–7.6) and median overall survival was 8.5 months (95% confidence interval, 3.1–17.4). A recently completed phase II trial in patients with microsatellite instability–high tumors (NCT03667170) provided confirmatory evidence of the efficacy of SC envafolimab, with an objective response rate of 42.7% at a dose of 150 mg QW [7].

Following a single SC administration in the dose-escalation phase, envafolimab could be detected in the serum of each patient for at least one time point at all dose levels. The maximum plasma concentration (C_{max}) and area under the curve (AUC) increased linearly over the dose range of 0.01–10 mg/kg (Fig. 2). At 0.3 mg/kg, two of three patients had a first-dose C_{max} that exceeded 0.5 μg/mL. The median time to reach C_{max} was 4–7 days. Neither first-dose C_{max} nor AUC were significantly affected by injection site (Fig. 3). During the dose-exploration phase, in which all patients received envafolimab 300 mg SC once every 4 weeks (Q4W), the mean C_{max} after the first dose was 14 μg/mL, and the median time to reach C_{max} was 3 days. The first-dose half-life was estimated to be 14 days, and at steady state (first day of cycle 5), the mean effective half-life was 23 days. Pharmacokinetics simulations estimated that most patients would attain steady state after five cycles and that >90% of those receiving envafolimab 300 mg once every 3 weeks (Q3W) and 400 mg Q4W would maintain trough concentration above 5 μg/mL (Table 1), which is at least 10-fold higher than the minimum pharmacologically active concentration (0.5 μg/mL [1]).

Antidrug antibodies (ADAs) were detected in 12 of the 28 patients, of whom 2 had pre-existing ADAs. The frequency of de novo ADA production (36%) is in the range reported for IV administered nivolumab and atezolizumab but higher than for pembrolizumab and cemiplimab [8]. For the 10 patients who developed ADAs following treatment, the median time to first detection was 4.1 weeks and the median duration of positivity was 4.1 weeks (Table 2). Nine of these patients had additional ADA data, of whom three had only negative tests and two had a negative test at the last assessment. Dose-normalized steady-state trough concentrations did not significantly differ between patients without and with ADAs, irrespective of when they were detected (Fig. 4).

These results provide data to select the dosing of SC envafolimab. When administered QW, SC envafolimab was safe up to the maximum administered dose of 10 mg/kg and was active at doses as low as 0.3 mg/kg. SC administration at a dose of 300 mg Q4W was also feasible and resulted in a similar tumor response and safety as SC administration of doses ≥0.3 mg/kg administered QW. As with other PD-1 and anti-PD-L1 antibodies [9], increasing the dose of envafolimab was not associated with an improvement in objective response or increased toxicity. These results support use of a fixed-dose schedule administered Q3W or Q4W for the future clinical development of SC envafolimab. In ongoing studies, 300 mg Q3W and 400 mg Q4W is being investigated.

This phase I study showed that SC injection of envafolimab at 200 mg/mL was an effective route of administration, was well tolerated, and had durable antitumor activity at a wide range of doses and schedules in patients with previously treated advanced solid tumors. A recent phase I trial of the humanized PD-1 monoclonal antibody PF-068-1591 showed that it was well tolerated and had antitumor activity when administered SC, although three separate 2-mL injections of 50 mg/mL were required to deliver the full dose [10]. Like envafolimab, SC administration of PF-068-1591 resulted in prolonged absorption (median time to C_{max} ~8 days). It also resulted in a lower C_{max} and correspondingly fewer grade ≥3 TEAEs than IV administration. Therefore, the slower absorption, lower C_{max}, and prolonged half-life of envafolimab may offer advantages over IV administration.

In conclusion, envafolimab is the first-in-class PD-1/PD-L1 antibody that can be administered at a therapeutic dose in a single SC injection of under 2 mL. As such, envafolimab has the potential to be a more convenient option than currently approved IV PD-1/PD-L1 inhibitors.

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Figures and Tables

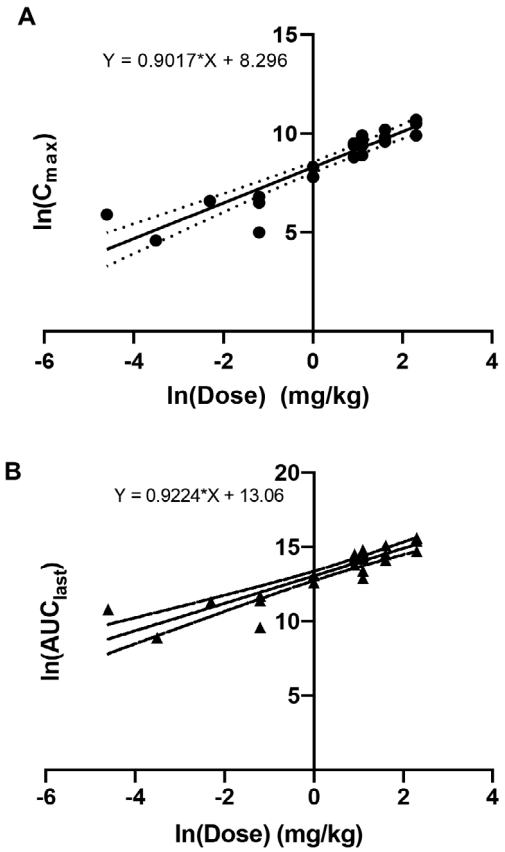

Figure 2. Relationship between natural log-transformed dose and C_{max} **(A)** and AUC_{last} **(B)**. Slopes were calculated by nonlinear regression analysis.
Abbreviations: AUC_{last}, area under the curve until the last measurement; C_{max}, maximum plasma concentration.

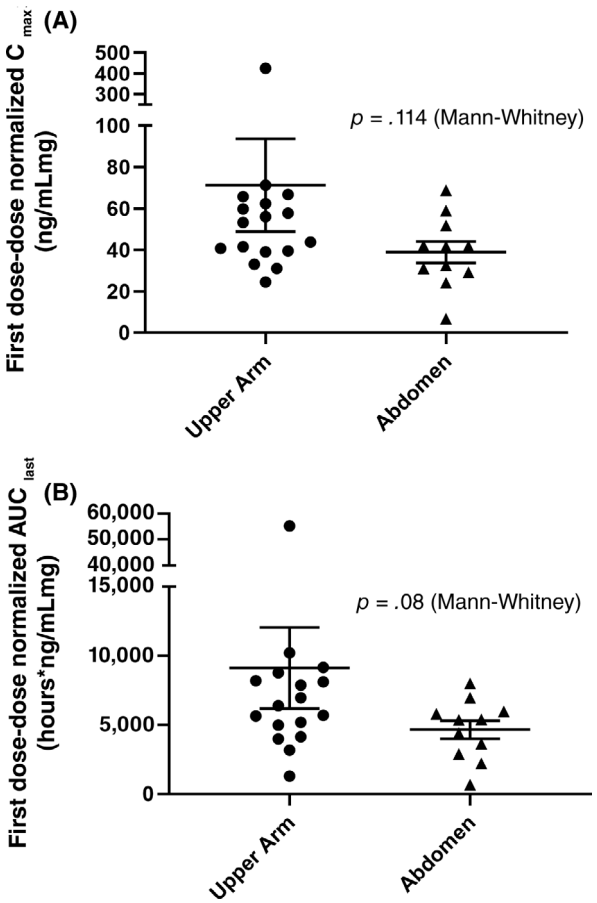

Figure 3. Effect of subcutaneous injection site on first-dose dose-normalized C_{max} **(A)** Or dose-normalized AUC_{last} **(B)**.
Abbreviations: AUC_{last}, area under the curve until the last measurement; C_{max}, maximum plasma concentration.

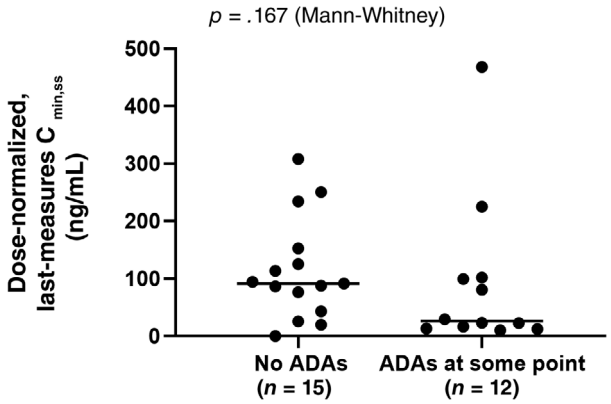

Figure 4. Dose-normalized steady-state serum concentrations of envafolimab in patients without and with antidrug antibodies. Abbreviations: ADA, antidrug antibody; $C_{min,ss}$, minimum serum concentration at steady state.

Table 2. Antidrug antibodies

Measure	Overall ADA analysis population ($n = 28$)
Baseline test result, *n* (%)	
Positive	2 (7)
Negative	26 (93)
Test result during treatment, *n* (%)	
Positive	12 (43)
Positive but negative at baseline	10 (36)
Time to positivity in participants negative at baseline, weeks	
Mean (SD)	3.6 (1.0)
Median	4.1
Min–max	2.0–4.4
Duration of positivity in participants negative at baseline, weeks	
Median	4.1
Min, max	0.14+, 31.14+
Participants who were negative at baseline, had a positive postbaseline test, and had ≥1 subsequent test result, *n* (%)	
Data available	9 (32)
All subsequent test results were negative	3 (11)
≥1 subsequent test result was positive	6 (21)
Last test was positive	4 (14)
Last test was negative	2 (7)