Investigational New Drugs (2022) 40:1021–1031
https://doi.org/10.1007/s10637-022-01287-7

RESEARCH

Phase I study of envafolimab (KN035), a novel subcutaneous single-domain anti-PD-L1 monoclonal antibody, in Japanese patients with advanced solid tumors

Toshio Shimizu[1,3] · Takako Eguchi Nakajima[2,4] · Noboru Yamamoto[1] · Kan Yonemori[1] · Takafumi Koyama[1] · Shunsuke Kondo[1] · Yu Sunakawa[2] · Naoki Izawa[2] · Yoshiki Horie[2] · Silong Xiang[5] · Siying Xu[5] · Lan Qin[5] · John Gong[5] · David Liu[5]

Received: 25 May 2022 / Accepted: 15 July 2022 / Published online: 6 August 2022

Abstract

Envafolimab is the first and only globally approved subcutaneously injectable PD-L1 antibody. This open-label, multicenter Phase 1 trial assessed the safety, tolerability, pharmacokinetic (PK) profile, and efficacy of envafolimab as a single agent in Japanese patients with advanced solid tumors. In the dose-escalation phase, 10 patients received subcutaneous (SC) envafolimab QW at 1.0 mg/kg, 2.5 mg/kg and 5.0 mg/kg. In the dose-expansion phase, 16 patients were treated at 2.5 or 5.0 mg/kg Q2W in part-1 and 9 patients received SC envafolimab 300 mg Q4W in part-2. No dose-limiting toxicities (DLTs) were reported. Envafolimab was well tolerated and no new safety signals were identified compared with other marketed products of the same class. Three patients reported Grade ≥ 3 envafolimab-related treatment-emergent adverse events (TEAE), including adrenal insufficiency, cerebral infarction, and immune-mediated enterocolitis. Envafolimab demonstrated dose-proportional increases in area under the time-concentration curve (AUC) and maximum serum concentration (C_{max}). The overall response rate (ORR) was 11.4% (n = 4) and disease control rate (DCR) was 34.3% (n = 12). Consistent with that observed in other envafolimab Phase 1 trials and approved PD-1/PD-L1 inhibitors, the safety profile of SC envafolimab in Japanese patients with advanced solid tumors was well tolerated with efficacy comparable to IV administered treatments. Pharmacokinetics data and preliminary anti-tumor response support dose regimens with longer dosing intervals (Q2W or Q4W). As such, envafolimab offers patients a more convenient treatment option than currently available intravenously administered PD-1/PD-L1 inhibitors.

ClinicalTrials.gov identifier NCT03248843(August 14, 2017).

Keywords Envafolimab · Subcutaneous · Programmed death-ligand 1 · Immunotherapy · Japanese

Introduction

Blockade of the PD-1/PD-L1 pathway with monoclonal antibodies (mAbs) has been a successful target of cancer immunotherapy in recent years. The approvals of PD-(L)1 inhibitors for treatment of multiple tumor indications worldwide have resulted in a treatment paradigm shift in immuno-oncology therapeutics, providing durable remissions for patients with cancer.

All other approved anti-PD-1/PD-L1 antibodies are administered intravenously (IV). Although some patients receiving these treatments achieve durable responses and long-term survival, the need for maintenance therapy requires repetitive IV infusions in the clinic/hospital. This results in a drain in personal productivity and time along

✉ Toshio Shimizu
sentants@wakayama-med.ac.jp

1 Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo 1040045, Japan

2 Department of Medical Oncology, St. Marianna University Hospital, Kawasaki 2168511, Japan

3 Department of Pulmonary Medicine and Medical Oncology, Graduate School of Medicine, Wakayama Medical University, Wakayama 6418509, Japan

4 Department of Early Clinical Development, Graduate School of Medicine, Kyoto University, Kyoto 6068507, Japan

5 3D Medicines Co., Ltd, Sichuan, China

with accumulating health care costs [1]. Subcutaneous (SC) administration of mAbs has become a valuable alternative to IV administration in oncology. Some SC monoclonal antibody formulations (eg, trastuzumab, rituximab and bortezomib) have shown safety and tolerability profiles and efficacy comparable to that of IV administered mAbs in the treatment of cancer [2–6]. Compared with IV administration, SC administration is associated with lower resource utilization and cost, greater patient treatment compliance, thereby providing potential benefit to patients and payers [7, 8]. However, despite the interest in developing SC mAbs, challenges hampering the successful application of SC administration have occurred in drug formulation, with issues such as high viscosity and aggregation, and the inherent immunogenicity of mAbs [9].

Envafolimab, also known as KN035, is a novel recombinant protein of a humanized single-domain anti-PD-L1 antibody fused with a human IgG1 Fc fragment [10]. It is the first and only globally approved subcutaneously injectable anti-PD-L1 antibody for previously treated microsatellite instability high (MSI-H)/mismatch repair deficiency (dMMR) advanced solid tumors in China [11]. The antibody portion of envafolimab was obtained from a focused phage library from peripheral blood mononuclear cells of a human PD-L1-immunized camel. Point mutations introduced in the Fc fragment decreased effector functions, including antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), thus reducing the IgG1-Fc-mediated toxicities. Envafolimab binds human PD-L1 with high affinity (Kd = 3 nM), blocks PD1-PD-L1 interaction, and stimulates T cell activation at concentrations below 0.5 μg/mL, thereby relieving the immunosuppressive effect and enhancing immune surveillance and cytotoxicity by T cells, leading to an anti-tumor immune response [10]. Envafolimab is more water soluble and more stable than conventional mAbs [10]. Because of its high solubility (200 mg/mL), the approved full therapeutic dose of envafolimab (150 mg, QW) can be administered SC in a single injection of 0.75 mL in less than 30 s and without the need for an adjuvant.

Three Phase 1 clinical trials in China, the US, and Japan were designed to evaluate the safety and tolerability of envafolimab, along with its recommended Phase 2 dose, and provide the foundation for future clinical development in different ethnic populations. Results from the study in US patients showed that SC envafolimab had a favorable safety and pharmacokinetic profile, with promising preliminary anti-tumor activity [12]. Results from the pivotal Phase 2 trial in Chinese patients showed that envafolimab was safe and effective in the treatment of previously treated advanced dMMR/MSI-H solid tumors [13]. Here, we report the results of the Phase 1 study in Japanese patients with locally advanced or metastatic solid tumors.

Methods

Patient population

Patients were eligible for inclusion if they were ≥ 18 years, had a histologically or cytologically confirmed solid tumor that was recurrent, metastatic, or refractory to at least one prior line of therapy and had no further standard treatment options. Eligible patients should have adequate renal, hepatic, bone marrow function and an ECOG performance status of 0 or 1. Patients were excluded from the study if they were on any concurrent anticancer treatment, had received prior anti-PD-L1 therapy, had a history of immune-mediated conditions including pneumonitis or interstitial lung disease, or were on active systemic corticosteroid usage > 10 mg/day. Women who were pregnant or lactating were excluded.

Study design and treatment

This was an open-label, multicenter, Phase 1 dose-escalation and dose-expansion clinical trial. In the dose escalation phase, patients received SC envafolimab QW with a DLT evaluation period of 28 days. For the QW schedule, traditional 3 + 3 design was followed and three dose levels of 1.0 mg/kg (n = 3), 2.5 mg/kg (n = 4), and 5.0 mg/kg (n = 3) were planned. The initial starting dose of 1.0 mg/kg QW was chosen based on the well-tolerated safety profile of envafolimab dosing at 0.01–1.0 mg/kg QW demonstrated in the two other phase 1 studies conducted in the United Stated and China. In the dose expansion part-1, 16 patients were treated at 2.5 or 5.0 mg/kg Q2W. After the completion of dose expansion part-1, a fixed dose regimen with a longer dosing interval (Q4W) was investigated, as no DLT was observed at doses ranging from .01-10.0 mg/kg QW and longer than expected half-life observed in the ongoing phase 1 studies. During part-2 of the dose expansion, nine patients received subcutaneous envafolimab 300 mg once every four weeks (Q4W).

Efficacy and safety outcomes

Safety evaluations to assess the primary endpoint of safety and tolerability were performed based on treatment-emergent adverse events (TEAEs) and dose-limiting toxicities (DLTs). Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events CTCAE v4.03.

Tumor response was assessed by investigators using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 every 12 weeks. Response confirmation was done with

imaging performed at least 4 weeks after the first documentation of response (complete response (CR) or partial response (PR)).

Pharmacokinetics and Immunogenicity Assessments

In the dose escalation phase and dose expansion phase of the study, full PK sampling was performed after the first dose of Cycle 1 (28 days) and sparse PK samples were collected at pre-dose and around C_{max} during the subsequent cycles. PK sampling timepoints are provided in supplementary file (SI. Table 1). Envafolimab concentrations were determined using a validated enzyme-linked immunosorbent assay-based assay. The resulting final-population PK model was used to perform simulations on virtual patients.

The immunogenicity of envafolimab was evaluated based on the development of anti-drug antibodies (ADAs) measured using a validated electrochemiluminescence bridging assay. Blood for anti-KN035 antibodies were to have been collected within 24 h before start of injection in Cycle 1, 2, 3 and 4, within 24 h before start of injection in every other subsequent cycle until Cycle 12, and at the mandatory Safety Follow-up Visit.

Statistical analysis

All patients treated with envafolimab were included in the safety analysis. PK and ADAs were analyzed in all patients who received at least one dose of envafolimab and had at least one concentration of envafolimab or ADAs measured. Safety, PK and immunogenicity data were summarized by descriptive statistics. The 95% confidence intervals (95%CIs) for ORR and DCR were calculated using the Clopper-Pearson method. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier product-limit method. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

From October 2017 to September 2019, 35 patients were enrolled in the study (Table 1). All subjects had received prior systemic anti-tumor drug therapies. The median age was 65 years, and 42.9% were male. Except for 1 patient whose clinical stage assessment could not be completed, all had Stage IV cancer (97.1%). 18 patients (51.4%) had an ECOG performance score ≥ 1. The most common (≥ 8%) types of cancer were esophageal (14.3%), pancreatic (8.6%) and soft tissue sarcoma (8.6%).

Patient disposition

All patients received at least one dose of envafolimab. The median total number of doses was 5 (range:1–118) (SI. Table 2). At the time of data cutoff (March 31, 2020), 33 of the 35 patients (94.3%) had discontinued treatment. The main reason for treatment discontinuation was disease progression (n = 27). 2 patients remained on treatment, at 1.0 mg/kg QW and 300 mg Q4W respectively. The median treatment duration was 9.7 weeks (range: 2 to 120 weeks). Five patients (14.3%) and 2 patients (5.7%) had treatment duration ≥ 6 months and 12 months, respectively.

Safety and tolerability

As of the data cutoff date, the majority of TEAEs reported during both phases of the study were mild to moderate in intensity and consistent with that reported in previous trials with envafolimab and other PD-L1/PD-1 mAbs (Table 2). The majority were considered related to drug, but did not lead to drug interruption or discontinuation. Overall there was no clear correlation between dose levels and safety. In the dose-escalation phase, no DLTs were reported and a maximum tolerated dose was not reached.

The most common TEAEs (occurring in ≥ 10% of the 35 treated patients in the safety analysis set) reported during both phases included rash, pruritus, pyrexia, nausea, vomiting, decreased appetite, and headache. One patient experienced a Grade 5 TEAE of thrombosis that was not considered related to drug. As expected, no infusion related reactions were reported.

As noted, the majority of reported TEAEs of all grades was considered drug-related (74.3%). The most frequently reported drug-related TEAEs occurring in ≥ 8% of patients included rash, pyrexia, pruritus, nausea, and blood thyroid stimulating hormone increased. Three patients reported Grade 3–4 drug-related TEAEs, including adrenal insufficiency, cerebral infarction, and immune-mediated enterocolitis. No Grade 5 drug-related TEAEs were reported. Four patients (11.4%) experienced drug-related TEAEs leading to treatment discontinuation, including hypoaesthesia, cerebral infarction, hepatic function abnormal, and immune-mediated enterocolitis.

Of the 6/35 (17.1%) patients with serious TEAEs, 4 patients experienced drug-related serious TEAEs of rash, adrenal insufficiency, immune-mediated enterocolitis, and cerebral infarction.

Overall, treatment-emergent adverse events of special interest (TEAESIs) were reported in 25/35 (71.4%) patients in the following 9 categories: gastrointestinal

Table 1 Patient Demographic and Clinical Characteristics at Baseline

Characteristic	Dose-escalation phase			Dose-expansion part-1		Dose-expansion part-2	
	1.0 mg/kg QW (N = 3)	2.5 mg/kg QW (N = 4)	5.0 mg/kg QW (N = 3)	2.5 mg/kg Q2W (N = 7)	5.0 mg/kg Q2W (N = 9)	300 mg Q4W (N = 9)	Total (N = 35)
Age (y), Median (range)	65 (46–66)	51.5 (38–65)	68 (49–75)	65 (40–78)	65 (35–72)	68 (31–74)	65 (31–78)
Sex, n (%)							
Male	1 (33.3)	3 (75.0)	1 (33.3)	1 (14.3)	4 (44.4)	5 (55.6)	15 (42.9)
Female	2 (66.7)	1 (25.0)	2 (66.7)	6 (85.7)	5 (55.6)	4 (44.4)	20 (57.1)
ECOG Performance Status, no. (%)							
0	2 (66.7)	3 (75.0)	2 (66.7)	2 (28.6)	3 (33.3)	5 (55.6)	17 (48.6)
1	1 (33.3)	1 (25.0)	1 (33.3)	5 (71.4)	6 (66.7)	4 (44.4)	18 (51.4)
Clinical stage[a], no. (%)							
IV	3 (100.0)	4 (100.0)	3 (100.0)	7 (100.0)	9 (100.0)	8 (88.9)	34 (97.1)
Number of prior systemic drug therapies, no. (%)							
1	0	0	0	0	0	1 (11.1)	1 (2.9)
2	0	1 (25.0)	1 (33.3)	0	3 (33.3)	2 (22.2	7 (20.0)
3	2 (66.7)	1 (25.0)	0	3 (42.9)	3 (33.3)	3 (33.3)	12 (34.3)
4	1 (33.3)	2 (50.0)	1 (33.3)	1 (14.3)	1 (11.1)	1 (11.1)	7 (20.0)
≥5	0	0	1 (33.3)	3 (42.9)	2 (22.2)	2 (22.2)	8 (22.9)

Distribution of tumor types: esophageal cancer in 5 patients (14.3%), pancreatic cancer and soft tissue sarcoma in 3 patients (8.6%) each, cervical cancer, colon cancer, intrahepatic bile duct cancer, neuroendocrine tumor, ovarian epithelial cancer and pelvis and urothelial carcinoma in 2 patients (5.7%) each, carcinoma of the appendix, duodenal cancer, extrahepatic bile duct cancer, gallbladder carcinoma, gastrointestinal stromal tumor, hepatocellular carcinoma, ovarian granular cell tumor, penis carcinoma, rectal cancer, thymic adenocarcinoma, peritoneal carcinoma, and carcinoma of unknown primary focus in 1 patient (2.9%) each

Data cutoff date: 31 Mar 2020

Percentages were calculated for each dose group and population based on the Safety Analysis Set

ECOG Eastern Cooperative Oncology Group

[a]One subject's clinical stage was not completed: the subject had penile cancer, and the investigator considered that it could not be staged according to this staging system

disorders, hepatic disorders, injection site reaction, hypersensitivity reactions, pneumonitis, endocrine disorders, cutaneous reactions, renal disorders, and infectious disorders (Table 2). TEAESIs reported in this study were consistent with that reported for other PD-L1/PD-1 inhibitors; most were drug-related but the majority were mild to moderate in severity. The incidence rate of injection site reactions was 14.3% (5/35), all of which were Grade 1–2.

In total, immune-related adverse reactions (irAEs) of all grades were reported in 13 (37.1%) and Grade 3–4 irAEs were reported in 2 (5.7%) patients. As of the data cutoff date, only 5 categories of irAEs were observed, including immune-related endocrine disorders (8 patients, 22.9%), immune-related skin adverse reactions (4 patients, 11.4%), immune-related neurological adverse events (1 patient, 2.9%), immune-related diarrhea and colitis (1 patient, 2.9%), and immune-related pneumonitis (1 patient, 2.9%). Most irAEs reported in this study were effectively managed with symptomatic treatment, dose interruption or discontinuation, and corticosteroids.

Pharmacokinetics

As shown in Table 3, following a single SC administration of envafolimab, the maximum serum concentration (C_{max}) and area under the curve (AUC) increased proportionally over the dose range (1.0–5.0 mg/kg QW, 2.5–5.0 mg/kg Q2W, and 300 mg Q4W).

In the dose-escalation phase, the median time to C_{max} ranged from 4 to 7 days.

In dose expansion part-1, the median T_{max} were 166 h and 118 h and the mean C_{max} were 11 μg/mL and 20 μg/mL in the 2.5 mg/kg Q2W and 5.0 mg/kg Q2W dose groups respectively. The AUC up to the last measured concentration (C336h) were 2347 h*μg/mL and 4986 h*μg/mL. No

Table 2 Summary of TEAEs

	No. (%)								
	Dose-escalation phase (N = 10)			Dose-expansion phase (N = 25)			Total (N = 35)		
Event	Any Grade	Grade 3/4	Grade 5	Any Grade	Grade 3/4	Grade 5	Any Grade	Grade 3/4	Grade 5
TEAE[a]									
Any	10 (100)	2 (20)	1 (10)	23(92)	5 (20)	0 (0)	33(94.3)	7 (20)	1 (2.9)
Drug-related[b]	8(80)	0 (0)	0 (0)	18(72)	3(12)	0 (0)	26(74.3)	3 (8.6)	0 (0)
Leading to drug interruption	2 (20)	0 (0)	0 (0)	5(20)	1(4)	0 (0)	7 (20)	1(2.9)	0 (0)
Leading to drug discontinuation	0 (0)	0 (0)	0 (0)	4 (16)	2 (8)	0(0)	4 (11.4)	2(5.7)	0 (0)
Serious TEAE	2 (20)	1 (10)	1(10)	4 (16)	3 (12)	0(0)	6 (17.1)	4 (11.4)	1 (2.9)
TEAE of special interest [c]									
Any	8 (80)	2 (20)	0 (0)	17(68)	1(4)	0 (0)	25(71.4)	3 (8.6)	0 (0)
Drug-related	7 (70)	0 (0)	0 (0)	13(52)	1(4)	0 (0)	20(57.1)	1(2.9)	0 (0)

Data cutoff date: 31 Mar 2020

Adverse event coding version: MedDRA 22.0; NCI CTC AE v4.03

[a] Defined as an adverse event that occurs from the first dose to 30 days after the last dose

[b] A study drug-related adverse event is defined as an adverse event assessed by the investigator to be definitely related and possibly related to the study drug

[c] According to the mechanism of immunotherapy, referring to immune-related adverse events reported with marketed anti-PD-1/PD-L1 antibodies, and considering local injection-related adverse events of the study drug

Table 3 Envafolimab Pharmacokinetic Parameters after the Single Dose Treatment

Dose and schedule	No. of Subjects	C_{max} (μg/mL), mean (CV)[a]	T_{max}, median (range)	AUC (h*μg/mL), mean (CV) [a,b]	$t_{½}$ median[a]	CL/F (L/h/kg), mean (CV) [a]	V_d/F (L/kg), mean (CV) [a]
Cycle 1, day 1							
1.0 mg/kg QW	3	3.1 (33.6%)	167.50 (94.33,168.02)	384 (41%)	-		-
2.5 mg/kg QW	4	12.7 (71.2%)	131.11 (94.77,167.50)	1661 (82%)	-	-	-
5.0 mg/kg QW	3	18.5 (2.79%)	94.90 (94.08,96.38)	2363 (2.15%)	-	-	-
2.5 mg/kg Q2W	7	12.0 (45.8%)	166.37 (71.78,167.98)	2506(40.5%)	691.0	0.0003 (50.2%)	0.279 (62.2%)
5.0 mg/kg Q2W	9	20.9 (29.4%)	118.17 (72.62,216.00)	5117(24.8%)	397.3	0.0003 (70.9%)	0.222 (30.1%)
300 mg Q4W	9	14.0 (27%)	166.62 (95.32,360.50)	6185 (26.2%)	321.4	-	-

AUC area under the curve, *CL/F* clearance; *Cmax*, maximum plasma concentration, *CV* coefficient of variation, *EHL* effective half-life tmax, time to maximum plasma concentration, *QW* weekl, *Q2W* every 2 weeks, *Q4W* every 4 weeks,—not evaluated

[a] Arithmetic means are presented because of low numbers in each group

[b] AUC until the last measurement

apparent changes in CL/F or Vd/F were found with the dose escalation from 2.5 mg/kg Q2W to 5.0 mg/kg Q2W.

After multiple doses of envafolimab in dose expansion part-1, the mean peak and trough concentrations on C3D1 were 15,533.34 ng/mL and 11,009.71 ng/mL for 2.5 mg/kg Q2W and 47,319.99 ng/mL and 26,486.98 ng/mL for 5.0 mg/kg Q2W, respectively.

In dose expansion part-2, after a single subcutaneous injection of envafolimab in the fixed dose cohort at 300 mg Q4W, the T_{max} was 166 h and the mean C_{max} was 13,541.86 ng/mL. The median $t_{1/2}$ was 321 h.

After multiple doses, the steady state tended to be reached on C4D1 in 1.0 mg/kg QW dose group, on C1D22 in 2.5 mg/kg QW dose group, on C2D1 in 5.0 mg/kg QW dose group, and on C3D1 based on simulated serum concentration–time data in 2.5 mg/kg Q2W, 5.0 mg/kg Q2W, and 300 mg Q4W dose groups. The median $t_{1/2}$ of envafolimab was 321 h after a single dose (C1D1, n = 9) and 430 h after multiple doses (C5D1, n = 1) in subjects of the 300 mg Q4W dose group. Overall, the steady state tended to be reached after 3–4 cycles of multiple doses (SI. Figure 1).

Table 4 Best Overall Response Rate (Confirmation required)

	1.0 mg/kg QW (N = 3) n (%)	2.5 mg/kg QW (N = 4) n (%)	5.0 mg/kg QW (N = 3) n (%)	2.5 mg/kg Q2W (N = 7) n (%)	5.0 mg/kg Q2W (N = 9) n (%)	300 mg Q4W (N = 9) n (%)	Overall (N = 35) n (%)
Best Overall Response							
Complete Response	0	0	0	0	0	0	0
Partial Response	1 (33.3)	0	0	0	2 (22.2)	1 (11.1)	4 (11.4)
Stable Disease	1 (33.3)	1 (25.0)	1 (33.3)	2 (28.6)	3 (33.3)	0	8 (22.9)
Progressive Disease	1 (33.3)	3 (75.0)	2 (66.7)	5 (71.4)	4 (44.4)	8 (88.9)	23 (65.7)
Not Evaluable	0	0	0	0	0	0	0
Objective Response Rate, % [95% CI]	1 (33.3) (0.8, 90.6)	0	0	0	2 (22.2) (2.8, 60.0)	1 (11.1) (0.3, 48.2)	4 (11.4) (3.2, 26.7)
Disease Control Rate, % [95% CI]	2 (66.7) (9.4, 99.2)	1 (25.0) (0.6, 80.6)	1 (33.3) (0.8, 90.6)	2 (28.6) (3.7, 71.0)	5 (55.6) (21.2, 86.3)	1 (11.1) (0.3, 48.2)	12 (34.3) (19.1, 52.2)

The 95% CI for ORR and DCR were calculated using exact Clopper-Pearson method

NE: Subject with NE are due to having no on-study tumor assessment

Data cutoff Date: 31-Mar-2020

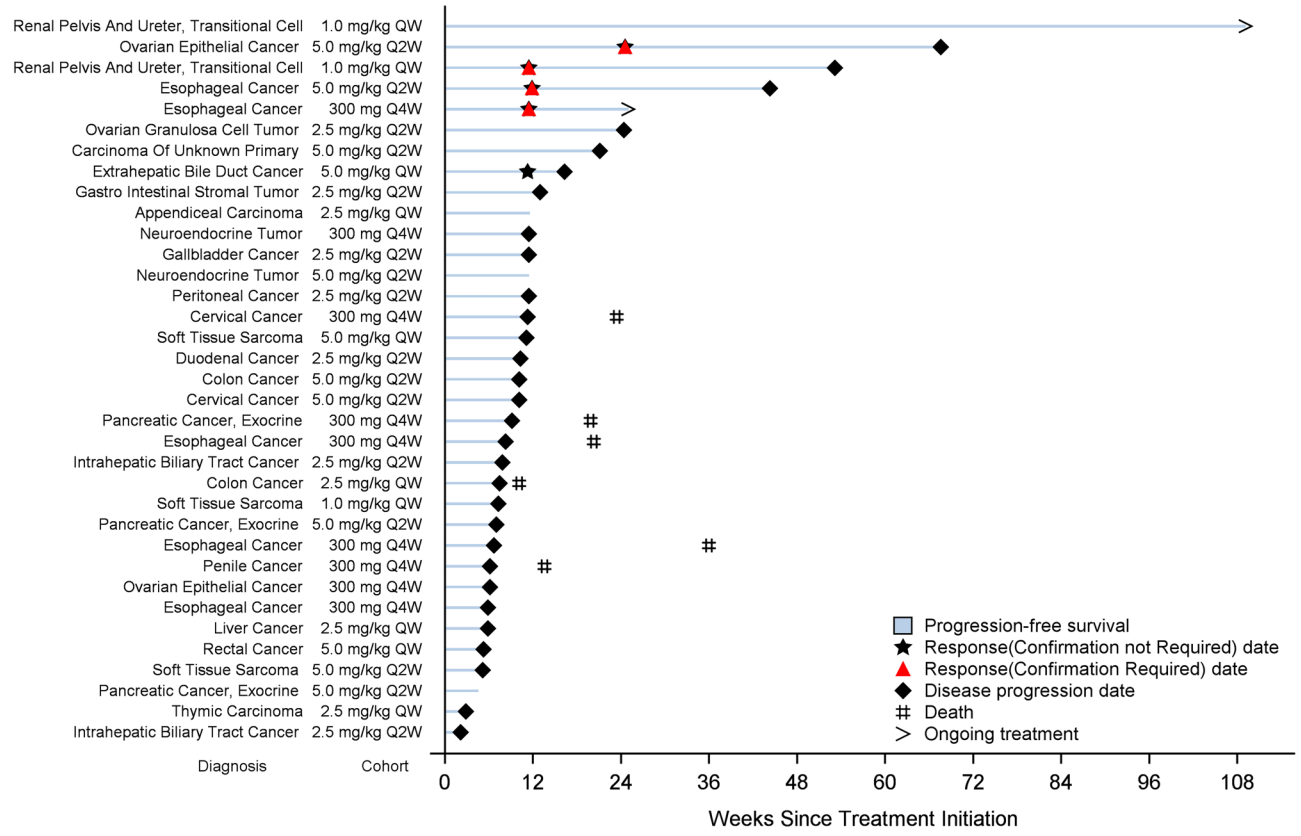

Fig. 1 Best Response and Duration of Response in all Treated Patients Abbreviations: PD, progressive disease; PR, partial response; QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SD, stable disease

Immunogenicity

Anti-drug antibodies (ADAs) results were available for all 35 patients, of whom 6 had pre-existing ADAs at baseline. Of the 35 patients, 18 (51.3%) patients had a positive ADA at least once post-baseline. Positive ADA measurements were transient in most patients and did not appear to affect PK exposure to envafolimab. As shown in Fig. 2, patients who developed ADA on treatment did not have reduced exposure as measured by dose normalized median trough concentration.

The median time to positive ADA measurement was 4.1 weeks (2.0 to 14.0 weeks) and the median duration of positive ADA was 8.14 weeks (0.14 + to 42.14 weeks) for all 18 patients. The incidence of positive ADA was the highest by Cycle 2 Day 1 (42.9%), which subsequently decreased over the time of treatment. By Cycle 6 Day 15, it had decreased to 2.9% for all patients. Additional ADA test results were available for 14 of the 18 patients: 5 had only negative results and 9 had at least one positive result. Of the 9, 3 patients had negative results and 6 patients still had positive results at the time of the last test.

Efficacy

Envafolimab as a single agent demonstrated preliminary durable anti-tumor activity in patients with advanced solid tumors in Japan. Efficacy was observed across different dose regimens (once a week, once every 2 weeks, or once every 4 weeks), and is consistent with the efficacy of other PD-1/PD-L1 antibodies as showed in Table 4.

As of data cutoff, PRs were reported in 5 (14.3%) patients including 4 confirmed PRs (1 each at 1.0 mg/kg QW, 300 mg Q4W, and 2 at 5.0 mg/kg Q2W) and 1 unconfirmed PR (5.0 mg/kg QW). Partial responses were observed in patients with urothelial carcinoma, extrahepatic bile duct cancer, ovarian cancer, soft tissue sarcoma and esophageal cancer. 1 patient with PR was still in continuous response by the time of database lock (Fig. 1). The median duration of response (DoR) was 41.9 weeks (95% CI: 5.1, 43.1). The DoR rates were 80.0% (95% CI: 20.4%, 96.9%) and 53.3% (95% CI: 6.8%,86.3%) at 6 and 9 months, respectively. 8 patients had a best overall response of stable disease (SD) and median duration of SD was 24.4 weeks (95%

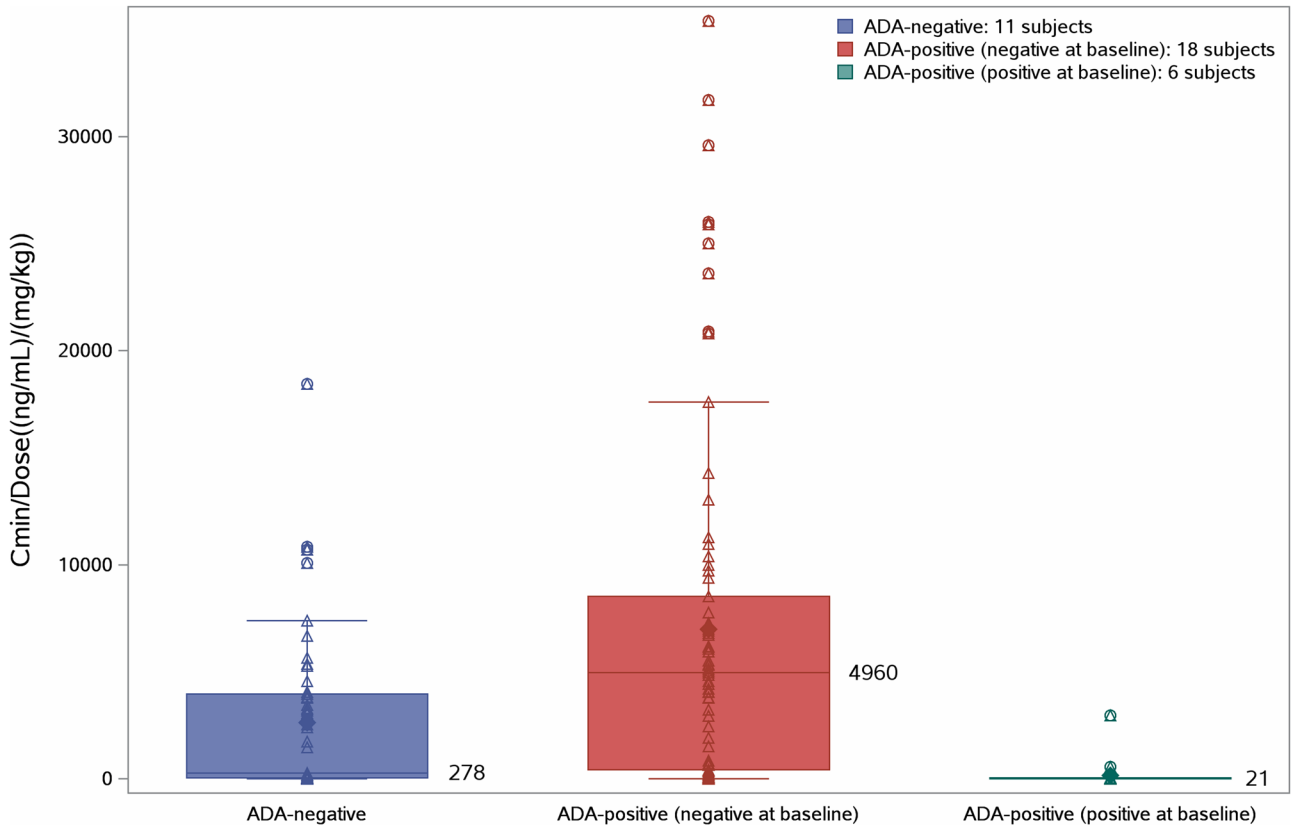

Fig. 2 Box-plot for Correlation of Dose Normalized Trough Concentrations to ADA

CI: 11.4, NE). Consistent with that reported with other anti-PD-1/PD-L1 antibodies in previously treated patients with advanced solid tumors, when only confirmed response was included, ORR was 11.4% (95% CI: 3.2%, 26.7%) and DCR was 34.3% (95% CI: 19.1%, 52.2%). The median time to response (TTR) was 11.4 weeks (95% CI: 11.3, 24.6), and approximately 50% of responders had a response at the time of the first response assessment.

As of the data cutoff date, 30 patients had progressed or died, with a median PFS of 2.4 months (95% CI: 1.7, 2.6). 6 deaths were recorded, and the median OS was not reached. The 6-month OS rate was 68.0% (95% CI: 37.5%, 86.0%), and the OS rate at 12 months was 54.4% (95% CI: 21.3%, 78.7%). Considering the limited sample size and number of events in this study, PFS and OS data need to be interpreted with caution.

Discussion

Envafolimab was granted conditional approval by China's National Medical Products Administration (NMPA) for the treatment of dMMR/MSI-H solid tumor based on a pivotal phase II trial (CN-006; NCT03667170) in November 2021. This is the first study to evaluate the safety, tolerability, and pharmacokinetics of envafolimab in the Japanese population. Results from this study demonstrate that SC administration of envafolimab was well tolerated and had durable antitumor activity in a wide range of doses across different regimens in Japanese patients with previously treated advanced solid tumors. Similar results have been reported in the previously reported Phase 1 studies in US patients (US-001; NCT02827968) and in the Chinese patients (CN-001; NCT03101488) [13].

A total of 35 patients in this study received at least one dose of envafolimab with a median treatment duration of 9.7 weeks (range: 2–120 weeks). 14.3% and 5.7% of patients were on treatment for ≥ 6 and 12 months, respectively.

Overall, the safety results from this trial were consistent with that previously reported in Phase 1 trials with envafolimab and other PD-1/PD-L1 antibodies in Japanese population [21–24] and non-Japanese population as well as in patients with solid tumors [13–16]. No DLTs and no new safety signals were reported. Most drug-related TEAEs were mild to moderate and did not lead to treatment discontinuation. No Grade 5 events were reported. The most frequently reported drug-related TEAEs (≥ 8%) included rash, pyrexia, pruritus, nausea, and blood thyroid stimulating hormone increased. The frequency, severity, and type

of irAEs reported in this trial were generally consistent with those observed with other PD-1/PD-L1 antibodies, and no irAE events specific to envafolimab were observed. Of note, no immune-related hepatitis and immune-related nephritis were reported in this study [17–20]. The incidence rate of injection site reactions was 14.3% (5/35), all of which were Grade 1–2.

This study showed preliminary anti-tumor activity of envafolimab in Japanese patients. The objective response rate observed in the current study was in line with the efficacy of other anti-PD-1/PD-L1 antibodies in Phase 1 studies in patients with previously treated patients with advanced solid tumors [14–17]. Responses to envafolimab were observed across multiple tumor types, including urothelial carcinoma, extrahepatic bile duct cancer, ovarian cancer, soft tissue sarcoma and esophageal cancer (Fig. 1).

Objective responses were observed in five patients including 1 unconfirmed PR across several dose cohorts. The mDoR were 41.9 weeks (5.1 to 43.1 weeks). One of five PR patients were still responding at the time of data cutoff. Stable disease was observed in 8 patients with various tumor types, including urothelial carcinoma, pancreatic cancer, and ovarian cancer. Objective response was first observed at 1.0 mg/kg QW. The proportions of PR did not increase significantly with the increase of dose, an observation also made with other anti-PD(L)-1 antibodies.

SC injection was an effective route of administration for envafolimab with a favorable PK profile. Following SC administration QW, exposure to envafolimab was dose-proportional. Based on the PK results from the US Phase 1 study ([13]), 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, which is at least tenfold higher than the minimum pharmacologically active concentration (0.5 μg/mL [10]). Response was also observed in regimens with longer dosing intervals with PR occurred at 5 mg/kg Q2W and 300 mg Q4W.

Consistent with that observed in other envafolimab Phase 1 trials and other approved PD-1/PD-L1 inhibitors, the safety profile of SC envafolimab in Japanese patients with advanced solid tumors was favorable and well tolerated with efficacy comparable to IV administered treatments. Pharmacokinetics data and preliminary anti-tumor response support dose regimens with longer dosing intervals (administered every 2 weeks or every 4 weeks). As such, envafolimab offers patients a potentially more convenient treatment option than currently available intravenously administered PD-1/PD-L1 inhibitors.

Many clinical trials investigating envafolimab are currently ongoing, including combination studies. Therefore, it is expected that envafolimab may become more widely used for the treatment of various cancer types.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10637-022-01287-7.

Acknowledgements We thank the participating patients, their family members, and all researchers involved in this study.

Author contributions All authors were involved in acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content. All authors gave final approval of the manuscript and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Funding This study was funded by 3D Medicines Co., Ltd, China.

Declarations

Competing interests Dr. Toshio Shimizu (TS) received research grants from 3D Medicine related to the submitted work; and research grants from Novartis, Eli Lilly, Loxo Oncology, Daiichi-Sankyo, AbbVie, Bristol-Myers Squibb, Eisai, AstraZeneca, Pfizer, Takeda Oncology, Incyte, Chordia Therapeutics, Symbio Pharmaceuticals, PharmaMar, Astellas; and advisory role fees from AbbVie, Daiichi-Sankyo, Takeda Oncology, Chordia Therapeutics; and personal fees (speakers) from Eli Lilly, Chugai Pharmaceutical Co., Taiho, Boehringer Ingelheim, MSD outside the submitted work.Dr. Noboru Yamamoto (NY) received research grants from Astellas, AstraZeneca, Chugai, Eisai, Taiho, BMS, Pfizer, Novartis, Eli Lilly, AbbVie, Daiichi-Sankyo, Bayer, Boehringer Ingelheim, Kyowa-Hakko Kirin, Takeda, ONO, Janssen Pharma, MSD, MERCK, GSK, Sumitomo Dainippon, Chiome Bioscience, Otsuka, Carna Biosciences, Genmab, Shionogi; and advisory role fees from Eisai, Takeda, Otsuka, Boehringer Ingelheim, Cimic, Chugai; and personal fees (speakers) from AstraZeneca, Eli Lilly, ONO, Chugai, Sysmex, Daiichi-Sankyo, Eisai outside the submitted work. Dr. Kan Yonemori (KY) received research grants from MSD, Daiichi-Sankyo, Astrazeneca, Taiho, Pfizer, Novartis, Takeda, Chugai, Ono, Sanofi, Seattle genetics, Eisai, Eli Lilly, Genmab, Boeringer Ingelheim, Kyowa Hakko Kirin, Nihon Kayaku, Haihe; and advisory role fees from Novartis, Eisai, AstraZeneca, Chugai, Takeda, Genmab, OncXerna; and personal fees from Pfizer, Eisai, AstraZeneca, Eli Lilly, Takeda, Chugai, Fuji Film Pharma outside the submitted work.Dr. Shunsuke Kondo (SK) received research grants from Takeda, AstraZeneca, Abbie, Eli Lilly, MSD, Boehringer Ingelheim, Chugai, Eisai, Incyte, Pfizer; and personal fees from Chugai, Incyte, Takeda, Chugai, Termo, and Eisai outside the submitted work.Dr. Takafumi Koyama (TK) received research grants from Novartis, Daiichi-Sankyo, Eli Lilly, PACT Pharma; and personal fees from Chugai and Sysmex outside the submitted work.Dr. NAKAJIMA reports grants and personal fees from Sumitomo Dainippon Pharma Co., personal fees from Boehringer Ingelheim , personal fees from Bristol-Myers Squibb, grants and personal fees from Ono Pharmaceutical Co., grants and personal fees from Taiho Pharmaceutical Co., personal fees from Amgen, grants and personal fees from Takeda Pharmaceutical Co., grants and personal fees from Chugai Pharmaceutical Co., grants and personal fees from Sanofi K.K., personal fees from Novartis Japan, grants and personal fees from Nippon Kayaku Co., grants and personal fees from MSD K.K., grants and personal fees from Eli Lilly Japan K.K., personal fees from Bayer Yakuhin, personal fees from Pfizer Japan Inc., personal fees from Daiichi Sankyo Co., personal fees from Yakult Honsha Co., personal fees from Nipro Co, personal fees from Merck Serono Co., grants from PAREXEL, grants from JCRO, grants from SHIONOGI & CO., LTD., personal fees from AstraZeneca, personal fees from IQVIA, personal fees from GlaxoSmithKline, outside the submitted work; Yu Sunakawa;Research funding and honoraria from Chugai Pharmaceutical, Taiho Pharmaceutical, Takeda, Eli Lilly Japan, and SanofiHonoraria from Bristol-

Myers Squibb Japan, Merck Biopharma, Ono Pharmaceutical, Bayer Yakuhin, MSD, Daiichi Sankyo, Sysmex and Guardant HealthNaoki Izawa:Honoraria from Taiho Pharmaceutical, Takeda, Eli Lilly Japan, and Bristol-Myers Squibb JapanYoshiki Horie:No. COISilong Xiang, Siying Xu, Lan Qin, John Gong, and David Liu are employees of and own stock in 3D Medicines Co., Ltd. JG and DL have leadership roles at 3D Medicines Co., Ltd.

References

1. Anderson KC, Landgren O, Arend RC, Chou J, Jacobs IA (2019) Humanistic and economic impact of subcutaneous versus intravenous administration of oncology biologics. Future Oncol 15(28):3267–3281. https://doi.org/10.2217/fon-2019-0368 (Epub 2019 Aug 9 PMID: 31394933)
2. Davies A, Merli F, Mihaljević B, Mercadal S, Siritanaratkul N, Solal-Céligny P, Boehnke A, Berge C, Genevray M, Zharkov A, Dixon M, Brewster M, Barrett M, MacDonald D (2017) Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. Lancet Haematol 4(6):e272–e282. https://doi.org/10.1016/S2352-3026(17)30078-9 (Epub 2017 May 2 PMID: 28476440)
3. Ismael G, Hegg R, Muehlbauer S, Heinzmann D, Lum B, Kim SB, Pienkowski T, Lichinitser M, Semiglazov V, Melichar B, Jackisch C (2012) Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-III breast cancer (HannaH study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol 13(9):869–878. https://doi.org/10.1016/S1470-2045(12)70329-7 (Epub 2012 Aug 9 PMID: 22884505)
4. Moreau P, Pylypenko H, Grosicki S, Karamanesht I, Leleu X, Grishunina M, Rekhtman G, Masliak Z, Robak T, Shubina A, Arnulf B, Kropff M, Cavet J, Esseltine DL, Feng H, Girgis S, van de Velde H, Deraedt W, Harousseau JL (2011) Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol 12(5):431-40. https://doi.org/10.1016/S1470-2045(11)70081-X. Epub 2011 Apr 18. Erratum in: Lancet Oncol. 2011 Jun;12(6):522. PMID: 21507715
5. Merz M, Salwender H, Haenel M, Mai EK, Bertsch U, Kunz C, Hielscher T, Blau IW, Scheid C, Hose D, Seckinger A, Jauch A, Hillengass J, Raab MS, Schurich B, Munder M, Schmidt-Wolf IG, Gerecke C, Lindemann HW, Zeis M, Goldschmidt H (2015) Subcutaneous versus intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial. Haematologica 100(7):964–969. https://doi.org/10.3324/haematol.2015.124347
6. Lugtenburg P, Avivi I, Berenschot H, Ilhan O, Marolleau JP, Nagler A, Rueda A, Tani M, Turgut M, Osborne S, Smith R, Pfreundschuh M (2017) Efficacy and safety of subcutaneous and intravenous rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in first-line diffuse large B-cell lymphoma: the randomized MabEase study. Haematologica 102(11):1913–1922. https://doi.org/10.3324/haematol.2017.173583. Epub 2017 Sep 21. PMID: 28935843; PMCID: PMC5664395
7. Franken MG, Kanters TA, Coenen JL, de Jong P, Koene HR, Lugtenburg PJ, Jager A, Uyl-de Groot CA (2018) Potential cost savings owing to the route of administration of oncology drugs: a microcosting study of intravenous and subcutaneous administration of trastuzumab and rituximab in the Netherlands. Anticancer Drugs 29(8):791–801. https://doi.org/10.1097/CAD.0000000000000648 (PMID: 29846248)
8. Franken M, Kanters T, Coenen J, de Jong P, Jager A, Groot CU (2020) Hospital-based or home-based administration of oncology drugs? A micro-costing study comparing healthcare and societal costs of hospital-based and home-based subcutaneous administration of trastuzumab. Breast. 52:71–77. https://doi.org/10.1016/j.breast.2020.05.001. Epub 2020 May 16. PMID: 32447129; PMCID: PMC7487951
9. Viola M, Sequeira J, Seiça R, Veiga F, Serra J, Santos AC, Ribeiro AJ (2018) Subcutaneous delivery of monoclonal antibodies: How do we get there? J Control Release 286:301–314. https://doi.org/10.1016/j.jconrel.2018.08.001 (Epub 2018 Aug 2 PMID: 30077735)
10. Zhang F, Wei H, Wang X, Bai Y, Wang P, Wu J, Jiang X, Wang Y, Cai H, Xu T, Zhou A (2017) Structural basis of a novel PD-L1 nanobody for immune checkpoint blockade. Cell discovery 3:17004. https://doi.org/10.1038/celldisc.2017.4
11. Envafolimab Injection (2021) Full prescribing information, 2021. NMPA, https://www.nmpa.gov.cn/datasearch/home-index.html
12. Papadopoulos KP, Harb W, Peer CJ, Hua Q, Xu S, Lu H, Lu N, He Y, Xu T, Dong R, Gong J, Liu D (2021) First-in-Human Phase I Study of Envafolimab, a Novel Subcutaneous Single-Domain Anti-PD-L1 Antibody, in Patients with Advanced Solid Tumors. Oncologist 26(9):e1514-e1525. https://doi.org/10.1002/onco.13817. Epub 2021 May 27. PMID: 33973293; PMCID: PMC8417852
13. Li J, Deng Y, Zhang W, Zhou A-P, Guo W, Yang J, Yuan Y, Zhu L, Qin S, Xiang S, Lu H, Gong J, Xu T, Liu D, Shen L (2021) Subcutaneous envafolimab monotherapy in patients with advanced defective mismatch repair/microsatellite instability high solid tumors. J Hematol Oncol 14:95. https://doi.org/10.1186/s13045-021-01095-1
14. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharfman WH, Anders RA, Taube JM, McMiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M (2012) Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366(26):2443–54. https://doi.org/10.1056/NEJMoa1200690. Epub 2012 Jun 2. PMID: 22658127; PMCID: PMC3544539
15. Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M, Drengler R, Chen C, Smith L, Espino G, Gergich K, Delgado L, Daud A, Lindia JA, Li XN, Pierce RH, Yearley JH, Wu D, Laterza O, Lehnert M, Iannone R, Tolcher AW (2015) Phase I Study of Pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors. Clin Cancer Res 21(19):4286–4293. https://doi.org/10.1158/1078-0432.CCR-14-2607 (Epub 2015 May 14 PMID: 25977344)
16. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M, Lamping E, Oyelakin I, Marté JL, Lepone LM, Donahue RN, Grenga I, Cuillerot JM, Neuteboom B, Heydebreck AV, Chin K, Schlom J, Gulley JL (2017) Avelumab for metastatic or locally advanced previously treated solid tumours (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol 18(5):587–598. https://doi.org/10.1016/S1470-2045(17)30239-5. Epub 2017 Mar 31. PMID: 28373007; PMCID: PMC6387686
17. TECENTRIQ®(atezolizumab). Full prescribing information. Genentech Oncology. 2021.; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761034s028lbl.pdf.
18. KEYTRUDA® (pembrolizumab). Full prescribing information. Merck Sharp & Dohme Corp. 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125514s125lbl.pdf
19. IMFINZIU® (durvalumab). Full prescribing information.AstraZeneca. 2021.; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761069s028lbl.pdf

20. OPDIVO® (nivolumab). Full prescribing information. Bristol-Myers Squibb Company. 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/225554s112lbl.pdf.
21. Shimizu T, Seto T, Hirai F, Takenoyama M, Nosaki K, Tsurutani J, Kaneda H, Iwasa T, Kawakami H, Noguchi K, Shimamoto T, Nakagawa K (2016) Phase 1 study of pembrolizumab (MK-3475; anti-PD-1 monoclonal antibody) in Japanese patients with advanced solid tumors. Invest New Drugs 34(3):347–354. https://doi.org/10.1007/s10637-016-0347-6. Epub 2016 Mar 22. PMID: 27000274; PMCID: PMC4859860
22. Fujiwara Y, Iguchi H, Yamamoto N, Hayama M, Nii M, Ueda S, Komuro K, Sugimoto M, Vlahovic G, Kozuki T (2019) Tolerability and efficacy of durvalumab in Japanese patients with advanced solid tumors. Cancer Sci 110(5):1715–1723. https://doi.org/10.1111/cas.14003. Epub 2019 Apr 13. PMID: 30891877; PMCID: PMC6501043
23. Mizugaki H, Yamamoto N, Murakami H, Kenmotsu H, Fujiwara Y, Ishida Y, Kawakami T, Takahashi T (2016) Phase I dose-finding study of monotherapy with atezolizumab, an engineered immunoglobulin monoclonal antibody targeting PD-L1, in Japanese patients with advanced solid tumors. Invest New Drugs 34(5):596–603. https://doi.org/10.1007/s10637-016-0371-6. Epub 2016 Jul 1. PMID: 27363843; PMCID: PMC5007272
24. Yamamoto N, Nokihara H, Yamada Y, Shibata T, Tamura Y, Seki Y, Honda K, Tanabe Y, Wakui H, Tamura T (2017) Phase I study of Nivolumab, an anti-PD-1 antibody, in patients with malignant solid tumors. Invest New Drugs 35(2):207–216. https://doi.org/10.1007/s10637-016-0411-2. Epub 2016 Dec 8. PMID: 27928714; PMCID: PMC5352798