Randomized phase II trial of survivin 2B peptide vaccination for patients with HLA-A24-positive pancreatic adenocarcinoma

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Abstract
The prognosis of advanced pancreatic adenocarcinoma is still extremely poor. This study sought to determine the efficacy of, and immunological response to, peptide vaccination therapy in patients with this disease. In this multicenter randomized phase II study, patients with advanced pancreatic adenocarcinoma after gemcitabine and/or tegafur/gimeracil/oteracil were randomly assigned to 3 groups that each received a 2-step treatment course. In Step 1, the groups received treatments of: (i) survivin 2B peptide (SVN-2B) plus interferon-β (IFN-β); (ii) SVN-2B only; or (iii) placebo until the patients show progression. In Step 2, all patients who consented to participate received 4 treatments with SVN-2B plus IFN-β. The primary endpoint was progression-free survival (PFS) after initiation of Step 1 treatment. Secondary endpoints included immunological effects assessed by analysis of PBMCs after Step 1. Eighty-three patients were randomly assigned to receive SVN-2B plus IFN-β (n = 30),
1 | INTRODUCTION

Pancreatic adenocarcinoma is the sixth most common malignancy in the United States; in Japan it also has a high mortality rate, being the fourth most common cause of cancer death1 (ganjyoho.jp, https://ganjyoho.jp/reg_stat/statistics/stat/summary.html). Recent advances in chemotherapy have improved overall survival (OS) among patients with pancreatic adenocarcinoma to some extent; however, mortality rates have not improved. Recently, treatment with immune checkpoint inhibitors (ICIs), including anti-programmed death-1 and anti-CTLA-associated protein-4, has achieved great success in several malignancies.2 However, the effectiveness of ICIs remains unsatisfactory, and severe side-effects have been reported. The ICI treatments induce antitumor immunity by canceling inhibitory effects on immunological effector CTLs, and only antigen-specific activation of CTLs can induce cancer-specific antitumor immunity. In this regard, peptide vaccination using antigenic peptides derived from tumor-associated antigens is an attractive approach for cancer immunotherapy.

Survivin belongs to the inhibitor of apoptosis protein family and is expressed in various types of malignancies, making it an attractive target molecule.3 We previously identified a human leucocyte antigen (HLA)-A24-restricted antigenic peptide (SVN-2B) from the survivin variant survivin 2B, and reported the efficacy of this peptide for several malignancies.4 In a phase I trial of peptide vaccination for colorectal cancer, breast cancer, bladder cancer, and oral cancer, we observed both reduction of tumor markers and tumor regression in some cases, indicating that peptide vaccination could be a promising approach for survivin-positive cancer.5 Furthermore, we undertook a phase I clinical trial using SVN-2B plus α-interferon (IFNα) for advanced pancreatic cancer.6 Although the number of cases was limited (n = 6), we observed good immune reaction for the SVN-2B peptide and a relatively good objective tumor response rate (ORR; 4 stable disease [SD] and 2 progressive disease [PD]), indicating that SVN-2B peptide vaccination with type 1 IFN could be a promising novel approach for pancreatic cancer. We therefore undertook this phase II clinical trial.

2 | MATERIALS AND METHODS

2.1 | Patients

Eligible patients had inoperable histologically diagnosed pancreatic adenocarcinoma and had been treated with at least first-line chemotherapy. Patients were required to have measurable disease, be HLA-A*24:02-positive, have histologically survivin protein-positive immunohistochemical (IHC) staining as described previously,7 aged from 20 to 85 years, and have an ECOG performance status of 0 or 1 and adequate bone marrow function and liver function. Patients whose cancer was refractory to gemcitabine or tegafur/gimeracil/oteracil (TS-1) and patients who were intolerant of gemcitabine and TS-1 were eligible.

2.2 | Study design and treatment

This was a multicenter, double-blinded, 3-arm randomized phase II trial of SVN-2B plus IFNβ carried out at Sapporo Medical University (Sapporo, Japan), The University of Tokyo (Tokyo, Japan), and Kanagawa Cancer Center (Kanagawa, Japan) among patients with advanced pancreatic adenocarcinoma after chemotherapy (Clinical trial registration number: UMIN 000012146). The study included 2 steps. In Step 1, patients were assigned to 3 arms in a ratio of 2:2:1, as follows: Arm 1, SVN-2B + IFNβ; Arm 2, SVN-2B; Arm 3, placebo. Survivin 2B peptide solution (1 mL; 1 mg/mL) was mixed with 1 mL incomplete Freund’s adjuvant (Montanide ISA-51 VG; Seppic) and emulsified, and 1.8 mL solution was injected s.c. every 2 weeks for Arm 1 and Arm 2 patients. One million units of IFNβ was dissolved in 1 mL saline and injected s.c. weekly for Arm 1 patients. Survivin 2B placebo (used for Arm 3 patients) was prepared as saline mixed with incomplete Freund’s adjuvant and emulsified. Interferon-β placebo (used for Arm 2 and Arm 3 patients) was prepared as 1 mL saline. In Step 1, patients were treated until diagnosed as having PD according to RECIST-PD or clinically apparent disease progression. In Step 2, all patients who consented to participate were treated with SVN-2B plus IFNβ until diagnosed with immune-related response.
criteria (iRRC) or irPD, or for a maximum of 7 months. The primary endpoint was progression-free survival (PFS) in Step 1, defined as the time from the date of first treatment to the date of death or disease progression. Secondary endpoints were the ORR according to RECIST⁸ and immunological reaction to SVN-2B peptide in Step 1. Other study outcomes included survivin expression in tumor tissue, the lymphocyte blast transformation test, PFS and ORR according to the iRRC criteria in Step 1 and Step 2,⁹ and safety.
2.3 | Assessment

The expressions of survivin and HLA class I were assessed by IHC staining using tumor tissue specimens as described previously.6,10 Tumor size was assessed every 6-8 weeks using computed tomography, with the first assessment occurring 8 weeks after the first treatment. The CTL response was assessed by tetramer assay and ELISpot assay before the trial, after Step 1, and after Step 2, as described previously.6

2.4 | Statistical analysis

We calculated that enrollment of 65 patients (in a ratio of 2:2:1) was required to achieve 73.1% power (α = 0.05) to estimate median survival of 5 months for the SVN-2B + IFNβ group (Arm 1) and 2 months for the placebo group (Arm 3), with a 7-month follow-up period and 24-month registration period, using Lakatos’ formula. The sample size for this study was defined as 71, in anticipation of some withdrawals. Unfortunately, 10 patients dropped out after registration but before receiving the first treatment, leaving a total of 94 patients enrolled.

The log rank test at α = 2.5% was used for PFS and survival post progression (SPP), and progression events included RECIST-PD and clinically apparent PD. Statistical analysis of the tetramer and enzyme-linked immunospot assays was intended to assess the results from patients who underwent immunological testing before treatment and after Steps 1 and 2. However, many patients unexpectedly experienced rapid worsening of performance status, including 11 patients in life-threatening condition, and 30 of the remaining 83 patients were unable to undergo immunological analysis during Step 1 (Figure 1A). Although a substantial number of patients underwent immunological testing as planned in Step 1, a very limited number of patients completed exploratory immunological testing in Step 2, and only 10 underwent immunological assays (Figure 1A). Unexpectedly, only 1 patient from the SVN-2B monotherapy group was available for immunological analysis in Step 2; this patient was excluded, and the exploratory analysis thus included the SVN-2B + IFNβ group (Arm 1; n = 4) and the placebo group (Arm 3; n = 5).

The t test, Dunnett’s test and Kruskal-Wallis test were used to evaluate the immunological response secondary endpoint. All statistical analyses were carried out with SAS software, version 9.4.

3 | RESULTS

3.1 | Patient profiles

The 94 patients who showed survivin- and HLA class I-positive by IHC staining (Figure 1B), enrolled in this study were randomly assigned to the study arms as follows: Arm 1, SVN-2B + IFNβ (n = 36); Arm 2, SVN-2B (n = 34); Arm 3, placebo (n = 19). Of these, 84 patients were treated between November 22, 2013 and October 27, 2016 (10 patients dropped out because of disease progression and 1 patient withdrew from the study before treatment; Figure 1A). All patients in the study died, with a median follow-up time of 101 days (range, 19-579 days). Patient characteristics are summarized in Table 1. All patients had primary and/or metastatic lesions and had received chemotherapy treatment before enrollment. Other previous treatments included surgery and radiation therapy. Thirty patients in the SVN-2B + IFNβ group, 34 in the SVN-2B group, and 19 in the placebo group completed Step 1 treatment; of these, immunological response could be analyzed for 18 patients in the SVN-2B + IFNβ group, 16 in the SVN-2B group, and 11 in the placebo group. Ten patients in the SVN-2B + IFNβ group, 12 in the SVN-2B group, and 7 in the placebo group consented to Step 2 treatment; exploratory analysis of immunological response was undertaken for 4 patients.

| TABLE 1 | Summary of data for patients with advanced pancreatic adenocarcinoma treated with survivin 2B peptide vaccination, alone or in combination with interferon-β (IFNβ), or placebo |
| Clinical variable | SVN2B + IFNβ, n = 36 | SVN2B, n = 34 | Placebo, n = 19 |
| Gender | Male : female | 19:11 | 21:13 | 13:6 |
| Age, years | Mean (min-max) | 62.0 (39-78) | 67.2 (29-82) | 63.9 (45-77) |
| ECOG PS | 0:1 | 21:9 | 24:10 | 14:5 |
| Prior surgery | Negative : positive | 18:12 | 20:14 | 10:9 |
| Prior radiation therapy | Negative : positive | 25:5 | 26:8 | 12:7 |
| Prior chemotherapy | Negative : positive | 0:30 | 0:34 | 0:19 |
| Histology | Adenocarcinoma : others | 28:2 | 32:2 | 17:2 |
| Stage at registration | I/III/IVa/IVb | 0:3:3:24 | 1:1:3:29 | 0:1:4:14 |
| Target lesion, mm | Mean (min-max) | 91.8 (24-226) | 86.6 (15-160) | 78.0 (10-156) |
| Primary lesion at registration | Negative : positive | 10:20 | 14:20 | 9:10 |
| Local lesions at registration | Negative : positive | 20:10 | 26:8 | 14:5 |
| Metastatic lesions at registration | Negative : positive | 3:27 | 4:30 | 3:16 |
| Local advanced disease at registration | Negative : positive | 13:17 | 19:15 | 6:13 |

max, maximum; min, minimum; PS, performance status.
patients in the SVN-2B + IFNβ group and 5 patients in the placebo group before and after administration of SVN-2B + IFNβ in Step 2.

### 3.2 Efficacy outcome and immune responses

During the study period, none of the enrolled patients received treatment other than peptide vaccinations. There was no statistically significant difference in PFS according to the RECIST criteria across the 3 groups (Figure 2A). In the exploratory analysis, there was also no difference across the 3 groups in OS (for the SVN-2B + IFNβ group, SVN-2B group, and placebo group, median [95% confidence interval (CI)] 102 days [77-144], 96.5 days [66-131], and 111 days [63-150], respectively; \( P = .4565 \)).

The disease control rate was evaluated according to the RECIST criteria. Stable disease was observed in 3 of 18 patients in the SVN-2B + IFNβ group, 5 of 15 in the SVN-2B group, and 3 of 11 in the placebo group. There was no significant difference in disease control rate across all groups.

Immune responses were evaluated by tetramer assay and enzyme-linked immunospot (ELISpot) assay using PBMCs from prevaccination and 8 weeks after the first vaccination. SVN-2B peptide-specific tetramer staining was increased after 8 weeks in the SVN-2B + IFNβ group; however, the difference did not reach statistical significance (\( P = .071 \); Figure 2B). There was no significant difference between pre- and posttreatment in the SVN-2B group or the placebo group (\( P = .9545 \) and \( P = .7947 \), respectively). The ELISpot assay revealed that SVN-2B peptide-specific IFNγ spots were significantly increased after treatment in the SVN-2B + IFNβ group (\( P = .0245 \)), and IFNγ spots were increased in the SVN-2B group, but this did not reach statistical significance.

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**FIGURE 2**  A, Kaplan-Meier estimates of progression-free survival among patients with advanced human leukocyte antigen-A24-positive pancreatic adenocarcinoma. Cytotoxic T lymphocyte frequencies pretreatment and posttreatment, by tetramer assay (B) and enzyme-linked immunospot (ELISpot) assay (C). Change in CTL frequency according to time course, by tetramer assay (D) and ELISpot assay (E). IFNβ, interferon-β; SVN-2B, survivin 2B peptide
There was no difference from pretreatment to posttreatment in the placebo group, as shown in Figure 2C (P = .6184). The increase in SVN-2B peptide-specific tetramer staining from before treatment to 8 weeks after initiation of Step 1 in the SVN-2B + IFNβ group was not significantly larger than that in the placebo group (P = .6670). In the SVN-2B group, the increase in tetramer staining also was not significantly higher than that in the placebo group (P = .5496). In the ELISpot assay, the increases in SVN-2B peptide-specific IFNγ spots were not significantly larger in the SVN-2B + IFNβ group or the SVN-2B group compared with the placebo group (P = .0849 and P = .5892, respectively).

In an exploratory analysis to investigate immunological effects during the period after Step 2 (the cases are summarized in Table S1), tetramer-positive cells were significantly increased at 8 weeks after Step 2 compared with before Step 1 (P = .0347) and before Step 2 (P = .0190) in the SVN-2B + IFNβ group, whereas there was no difference in the placebo group (Figure 2D). In the ELISpot assay, there was no significant difference between 8 weeks after Step 2 and before Step 1 (Figure 2E). A very small number of SVN-2B peptide-specific IFNγ spots were observed before Step 1 in the SVN-2B + IFNβ group, but some patients had a large number of spots at 8 weeks after Step 2. Swimmer plots showing SPP and PFS in each period (Step 1/Step 2) are shown in Figure 3. The median PFS for Step 2 was 69 days (range, 59-74 days). There was no significant difference in PFS between the SVN-2B + IFNβ group and the placebo group (median [95% CI], 66 days [63-70] vs 70 days [59-74]; P = .2617). Survival post progression was significantly better in the SVN-2B + IFNβ group than in the placebo group (median [95% CI], 312 days [43-460] vs 39 days [13-153]; P = .0318) (Figure S2).

### 3.3 Safety

Forty-one adverse events occurred with SVN-2B use, and 46 adverse events occurred with IFNβ use. Treatment-related adverse events, which occurred in over 5% of patients, were injection site reaction and fever. In the SVN-2B + IFNβ group, SVN-2B group, and placebo group, injection site reactions were observed in 15/30 patients (50.0%), 14/34 patients (41.2%), and 8/20 patients (40.0%), respectively; fever was observed in 3/30 patients (10.0%) in the SVN-2B + IFNβ group, but did not occur in the SVN-2B group or placebo group. Eighty-seven severe adverse events (over grade 3) were observed in the SVN-2B + IFNβ group, SVN-2B group, and placebo group in 20 patients (41.7%), 16 patients (33.3%), and 12 patients (25.0%), respectively; events included disseminated intravascular coagulation and multiple organ dysfunction, mainly caused by disease progression and loss of PS. There were no treatment-related severe adverse events.

### 4 Discussion

In this study, a 3-armed double-blinded placebo-controlled randomized phase II trial of SVN-2B peptide vaccine was undertaken among patients with HLA-A24-positive pancreatic cancer. In a previous study, we carried out a phase I trial of SVN-2B peptide vaccination with IFNα in patients with HLA-A24-positive advanced pancreatic cancer (n = 6), and observed promising results, including a 66.7% ORR rate according to RECIST (4 SD cases and 2 PD cases). In addition, type 1 IFN (IFNα) was found to enhance the immunological (CTL) reaction to peptide vaccination. We therefore concluded type 1 IFN is beneficial for CTL induction. However,
IFNα requires a relative higher amount for CTL induction compared with IFNβ, which brings higher rates of adverse effects including fever, bleeding tendency, and depression. Furthermore, IFNβ has been approved for s.c. injection in melanoma cases, as we used in this clinical trial. In this regard, we decided to use IFNβ in this study.

In the present study, we aimed to confirm the enhancement of peptide vaccination by type 1 IFN. By examining prevaccination vs postvaccination peripheral blood, we showed that type 1 IFN (IFNβ) enhanced the immunological reaction significantly. Thus, type 1 IFN is an appropriate adjuvant for peptide vaccination therapy. In this study, we applied a 2-step peptide vaccination protocol, because the antitumor effects of cancer immunotherapy are frequently delayed after immunization. The majority of patients in the phase II study showed progression after Step 1 and shorter OS compared with the phase I study result (median, 3.48 months vs 8.08 months), suggesting that patients with very advanced disease were enrolled in this study. However, among the limited number of patients who completed Step 2 treatment, those treated with SVN-2B + IFNβ showed longer survival compared with placebo-treated patients, indicating that a longer peptide vaccination protocol might be beneficial for pancreatic adenocarcinoma. The adverse effects experienced by patients in this study were limited and tolerable, including localized rash and fever; thus, SVN-2B + IFNβ peptide vaccination therapy appears to be safe and is feasible for further analysis. As this study suggests that longer vaccination might be beneficial for pancreatic cancer patients, peptide vaccination at early stages or adjuvant setting for prevention of recurrence might be a better approach than for patients in advanced stages.

Recently, personalized RNA mutanome vaccines based on gene mutations found in the exome sequences of patients with cancer were shown to be feasible and safe, and to possibly bring survival benefit.

Neoantigens developed from gene mutations are expected to be highly immunogenic; however, immunological reactions to neoantigens in patients with cancer have not been high without active immunization. In this study, we used SVN-2B peptide derived from survivin protein. Because survivin is an over-expressed antigen, the immunological reaction to SVN-2B should be low without active immunization. Thus, type 1 interferon could be a promising candidate adjuvant for peptide vaccination therapy.

Recent analyses of patients treated with immune checkpoint inhibitors have suggested that high tumor mutation burden is a predictor of better prognosis, and neoantigen expression is related to long-term survival in pancreatic cancer. Although there is no direct evidence that neoantigens derived from tumor mutations are related to antipancreatic cancer immunity, these observations indicate that gene mutations are related to antitumor immune reactions. Because pancreatic cancers are known to contain relatively few gene mutations, neoantigens for application in pancreatic cancer immunotherapy might be limited. Expression of survivin, which is expressed in pancreatic adenocarcinoma cells at a high rate (88%), is related to proliferation index, and high survivin expression is related to poorer prognosis, indicating that survivin is a reasonable target for pancreatic cancer immunotherapy.

In summary, we show that SVN-2B + IFNβ peptide vaccination therapy is safe and feasible for patients with pancreatic cancer, and IFNβ is a promising adjuvant for peptide vaccination therapy. Longer treatments with SVN-2B + IFNβ could be beneficial.

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DISCLOSURE

The authors have no conflict of interest in regard to this study.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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