Author’s response to reviews

Title: A double-blind randomized comparative clinical trial to evaluate the safety and efficacy of dendritic cell vaccine loaded with WT1 peptides (TLP0-001) in combination with S-1 in patients with advanced pancreatic cancer refractory to standard chemotherapy

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Author’s response to reviews:

Reply to Reviewer #1

1. Detailed reports of this complex trial. The endpoints, criteria of inclusion and exclusion are and specific, and the process to set sample size and randomization is specific. It's appropriate for your original design to evaluate the efficacy and safety of this vaccine. However, if your aim is to adopt TLP0-001 as a secondary therapy like presented in the last paragraph of background, whether it need to add the content of comparison between TLP0-001 and S-1. I would consider focusing on this perspective.

Thank you for your comment. S-1 is frequently used as a secondary treatment in Japan, however, the effectiveness of S-1 is not satisfactory. In this study, as we mentioned in discussion section (P.25, L.1-L.3), we developed a new regimen that combines TLP0-001 with S-1 for patients with advanced/recurrent pancreatic cancer refractory or intolerant to standard chemotherapy. Therefore, the aim of this study (P.8, L.8-L13) is to evaluate the safety and efficacy (as measured by OS) of TLP0-001 in patients with pancreatic cancer refractory or intolerant to standard therapy through a comparison of the control group (placebo in combination with S-1) and the investigational product group (TLP0-001 in combination with S-1).

To avoid the confusion, we modified the sentences of background as follows, “secondary → novel” (P.8,L.4).

2. Besides, I think it would be better to limit the adjuvant therapy (analgesia, nutrition support…).

Thank you for your comment. The primary endpoint of this study is OS and the main secondary endpoints are PFS and cytoreductive effect. Therefore, the outcomes evaluating these endpoints don’t seem to be influenced by limiting the adjuvant therapies. Moreover, this is RCT trial and the patients will be randomly allocated to either the investigational product group or the control group. Hence, the patients using analgesia and nutrition support would be randomly allocated. We don’t think limiting the adjuvant therapy is necessary.
Reply to Reviewer #2

1. As the authors described, this is the first-in human clinical trial of TLP0-001. I think the authors have investigated the safety of the vaccine before this trial. So, they should describe it in the Background or Discussion section.

Thank you for your comment. This is the first-in-human clinical trial of TLP0-001. Therefore, the trial will be performed with full consideration of safety as we mentioned in discussion section (P.25, L.14-P.26, L.4). To fully assure the safety of the subjects, an interim analysis will be performed when the first six patients of the investigational product group (TLP0-001 in combination with S-1) have completed the first course of treatment, and the safety for the continuation of the trial will be evaluated by the independent Data and Safety Monitoring Committee. The trial is only to be conducted at the Second Department of Surgery at Wakayama Medical University until the safety of the first course has been confirmed by the interim analysis. The procedure requires at least overnight hospitalization from Day 1 for observation.

On the other hand, some results of clinical trials evaluating the efficacy and safety of dendritic cell vaccine loaded with WT1 peptides were reported. The results of these reports were described in background section (P.7, L.14-P.8, L.2) as follows:

“a retrospective study of a dendritic cell vaccine loaded with WT1 peptides in combination with chemotherapy in patients with advanced pancreatic cancer suggested that survival was prolonged without serious adverse events [16]. Furthermore, other clinical studies of dendritic cell vaccine loaded with WT1 peptides in combination with chemotherapy in patients with advanced pancreatic cancer have confirmed the safety of administration of the vaccine and suggested that antiproliferative effect on the tumor and the survival-promoting effect were greater in patients with a positive immune response [17, 18].”

2. Also, this is the first trial of TLP0-001 combined with S-1. The authors should describe how they decided the administration dose of S-1. Did the authors have the results of dose escalation study?

Thank you for your valuable comment.

Cancer vaccines are believed to cause antitumor activity by inducing cancer antigen-specific cytotoxic T lymphocytes (CTL) as their mechanism of action. On the other hand, it is reportedly difficult for cancer vaccines to identify the recommended dose by the dose escalation design, because the vaccine dose-dependent increased induction of CTL is mostly not observed. Therefore, we considered that dosage and administration interval of TLP0-001 should be determined as the method which can certainly induce WT1 specific CTL.

We now added the following sentence in discussion section (P.25, L.4-L.9);
“In a preliminary clinical trial conducted with administration of dendritic cell loaded with WT1 peptides, 1×10^7 living dendritic cells were administered intradermally every other week [17]. In this study, five of six patients (83.3%) confirmed the increased induction of WT1 specific CTL after administration of dendritic cells. TLP0-001 is also considered to cause antitumor activity by inducing WT1 specific CTL and as a result of this preliminary clinical trial the dosage and administration interval of TLP0-001 were determined.”

3. How did the authors randomize the patients? Please describe the factors that were used for the adjustment of the patients.

Thank you for your comment. As we described in study design (P.9, L.14-L.15), allocation adjustment factors are institution and time of initial apheresis (before, during, or after primary treatment).

4. Are there any provision of surgical options in the protocol, if the tumor decreases and can be resected.

Thank you for your valuable comment. One of the selection criteria of our trial is patients who are assessed as refractory or intolerant after receiving therapy including gemcitabine plus nab-paclitaxel. We don’t prescribe surgical options in the protocol, because there is no clear evidence on the efficacy of surgery for the tumor which is decreased to be resectable after treatment. However, as shown in the treatment discontinuation criteria (P.11, L9), it is possible to discontinue the trial treatment when a patient requests to withdraw from the trial or a principal investigator judges that discontinuation of the study treatment is needed. Therefore, when the patient and the principal investigator select surgical treatment, we think it is possible to perform surgical treatment after discontinuation of trial treatment.

Reply to Reviewer #3

1. Include a section describing the statistical methods that will be used to analyze the primary and secondary outcomes as well as any subgroup analyses.

2. Will you be conducting the primary analysis on the ITT population?

Thank you for your valuable comments. We completely agree with the suggestion. We added following sentence as statistical analysis section (P.22, L.10-P.23, L.3);
“Statistical analysis

The primary population for efficacy analysis will be the full analysis set, defined as the patients who are administrated investigational product or placebo at least once. The primary endpoint is OS, defined as the time from date of secondary registration to the date of death from any cause. PFS is counted from the date of secondary registration to the date of death without progression, or of progression as confirmed by the Diagnostic Radiology Committee. OS and PFS will be compared using a stratified log-rank test with a two-sided alpha of 0.05 stratified by institution and time of initial apheresis (before, during, or after primary treatment). The HRs and 80% and 95% confidence intervals (CIs) will be estimated by the Cox proportional hazards model. Survival estimation will be also carried out using the Harrington-Fleming test, with the weight proportional to cumulative death probability. For the analysis of cytoreductive effect, adverse events and side effects, categorical outcomes will be summarized using frequency and percentage for each arm and will be compared using Fisher’s exact method. Besides, the odds ratios and 95% CIs will be estimated.”

3. Please clearly refer to the SPIRIT figure as a SPIRIT figure in the figure label as well as in the text of the manuscript.

Thank you for your valuable suggestion. We referred to the SPIRIT figure as a SPIRIT figure in the figure label as well as in the text of the manuscript.