Author's response to reviews

Title: Transperineal prostate brachytherapy, using I-125 seed with or without adjuvant androgen deprivation, in patients with intermediate-risk prostate cancer: study protocol for a phase III, multicenter, randomized, controlled trial

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Author's response to reviews: see over
1. It would help if the authors included a figure of the study schema. The current figure is of little use. I would delete it.

   - We have replaced the figure with a new one illustrating the entire study schema as suggested. This figure is inserted in the Methods/Design section as follows,

     Methods/Design, Page 8, Study design, Line 2

   - Study design

     The present investigation is a phase III, multicenter, randomized, controlled study of ADT and TPPB for patients with untreated intermediate-risk PCa (Figure 1).

2. Reference (5) is near the beginning of a paragraph, however, almost the entire paragraph is related to reference (5). I would move reference (5) to after sentence

   - We have moved reference (5) to the end of the entire paragraph as suggested.

3. Furthermore, symptoms persisted?

   - Introduction, Page 6, Line 2

   - To clarify the meaning, the sentence now reads “Furthermore, symptoms persisted after radiotherapy for up to two years despite <1 year of ADT (5).”

4. Despite the authors’ rationalization why 3 months of ADT is given to all study participants. I still do not understand nor do I agree with it. The use of ADT in this setting may skew results albeit for both group, but I still wonder, do we even need the initial 3 months of ADT?

   - We appreciate this comment much. This was indeed what we the organizing committee discussed extensively and debated at the time of planning. The reasons of
our decision are multifold. 1) Most institution had a long waiting list of patients when TPPB was introduced in Japan 7 years ago. It was felt impractical to have protocol without neoadjuvant ADT. There was a concern such a practice without neoadjuvant therapy could indeed slow the speed of enrollment. 2) The pure impact of short-term neoadjuvant therapy has not been established to date. All the retrospective studies to date failed to control the term and indication of additional endocrine manipulation both in neoadjuvant and adjuvant setting. If there are no solid rules, some patients with big glands can have 3-12 month longer endocrine manipulation for the purpose of downsizing and others don’t since their glands are small. This can potentially skew and bias the randomized scheme. We attempted to minimize the risk of inhomogeneity of the patient population in this randomized trial. The future trial may incorporate such treatment arm without neoadjuvant therapy. But this is, of course, up to the findings of this 0804 study.

- We rephrased the paragraph in the Discussion as follows,

  Discussion, Page 15, Paragraph 2, Line 3

  The ABS recommends neoadjuvant ADT in conjunction with TPPB for downsizing the prostatic gland when the initial size surpasses 60cc, but provides no clear indication for using ADT adjuvantly in intermediate- to high-risk disease. The liberal use of neoadjuvant therapy can be a confounder when evaluating efficacy of ADT in combination with TPPB within a certain risk category. The uniformly used neoadjuvant ADT and the consequent downsizing of the gland will facilitate recruitment and reduce potential bias in patient selection in our randomized trial. Since the participating institutions were overloaded with a long waiting list of patients for TPPB, it was considered more practical to have certain period of neoadjuvant ADT prior to TPPB. All patients are
thus planned to undergo fixed-term, 3-month neoadjuvant ADT.

5. I think the addition of prostate biopsies after therapy greatly strengthens the proposal. I am unsure why this part of the protocol has a different title. I would have thought the biopsies could have been a sub-aim in 804.

- I agree with this comment. This information can provide the basis of more thorough understanding of the tumor biology after TPPB. Unfortunately, the protocol board could not reach consensus on this issue. Some investigators raised the issue of associated morbidity potentially without any benefit to patient care. This did not allow us to evaluate biopsy findings under this prospective randomized scheme. Thus, we decided to conduct this part of investigation under exploratory manner, separate from the main 0804 study, under the different code. The description in the text was made accordingly.

- We added and rephrase the sentences in the Discussion as follows,

Discussion, Page 17, Line 10

In our correlative study (SHIP36B), histological effects of $^{125}$I-TPPB and ADT in relation to PSA levels and kinetics will be investigated separately. This exploratory design was determined since the organizing committee could not reach the consensus to investigate its impact under randomized scheme. Nevertheless, SHIP36B will provide important further information about the prognostic implication of PSA levels in intermediate-risk PCa patients treated with $^{125}$I-TPPB.