Author’s response to reviews

Title: Toremifene, a selective estrogen receptor modulator, significantly improved biochemical recurrence in bone metastatic prostate cancer: a randomized controlled phase IIA trial

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Author’s response to reviews:

We appreciate the comments and constructive criticisms of the reviewers regarding our manuscript. Changes and additions to our manuscript have been made to address their concerns.

Referees’ comments and responses

Reviewer: 1

Comments

In general, the quality of written English is acceptable; however the manuscript does contain some typos. For instance page 3/line 10 ("preliminary"), page 5/line 10 ("clinical trial phase IIA trial"), page 11/line 10 ("therapy"), page 12/line 13 ("also"). This needs to be corrected.
Response

Thank you for the helpful advice. I have corrected the typos.

Comments

Has the ER status determined in tumor samples of patients? This could provide important additional information.

Response

We investigated immunohistochemistry using AR, ERα and ERβ antibody. Labeling index (LI) was determined by counting the percentage of cells with positive immunoreactivity in 1,000 cells [18]. I have added the data to Table 1 and new Figure 2. LI of AR, ERα, and ERβ did not show statistical difference among three groups. In addition, LI of AR, ERα, and ERβ was not correlated with BCR by univariate Cox proportional hazard regression models (Table 3).

Comment

Despite the clinical relevance and adequate design of this work, the small patient number (n=15) is clearly insufficient to support the conclusions drawn from the presented data.

Response

This analysis is limited as a preliminary result in a single center. We conducted another clinical trial to confirm this combination therapy.

Reviewer #2

Comment

This study explored the effects of additional selective estrogen receptor modulators (SERMs) on the durability of androgen-deprivation therapy (ADT). Fifteen subjects were divided into 3 groups, the sample size is relative small, and the results need to be validated in the other studies. I have some major concerns:

1. In the statistical analyses part, the author mentioned "BCR-free survival curves were plotted using Kaplan-Meier method and verified using the log-rank test". I do not think it is enough for this study. The author should do univariate and multivariate Cox proportional hazards regression models to check the hazard ratios among these three groups.
Response

I have added Table 3 showing univariate Cox proportional hazard regression models. TOPADT was only found to be significant in the univariate analysis (p = 0.023, hazard ratio; 1.1e-9).

2. In Table 1, the author should add one more column for the P value to test the difference of variables among the three groups, and then make corresponding changes in the statistical methods.

Response

I have added the data of Wilcoxon rank-sum test and chi-square test for comparison among three groups.

3. For the explanation of the results shown in the Figure 2: p=0.04, ADT v.s. TOPADT, p = 0.48, ADT v.s. RAPADT, and p = 0.12, TOPADT v.s. RAPADT. There was no significant difference between TOPADT and RAPADT on the BCR-free rate. Could the author explain why RAPADT does not have the same effect as TOPADT?

Response

We discussed that there was no significant difference between TOPADT and RAPADT on the BCR-free rate (pages 16, lines 14 to pages 17 lines 2).

The reason why tumor inhibitory effect was different between TOPADT and RAPADT may be associated with the potency of the drugs and the pattern of ER expression in PC cells. Tumor-inhibitory effect of fulvestrant, another ERβ modulator, was limited because median time to progression was only 4.3 months in men with CRPC treated with fulvestrant [33]. Further investigations of additional ERβ modulators are warranted with regard to their potential role in the inhibition of human PC.

4. There are 6 figures in Figure 3, however, the legend of Figure 3 only described A and B. For the Figure B, C, D, E, and F, the p values should be presented like that in Figure A.

Response

I have revised Figure legends and added p values.