Peer Review File

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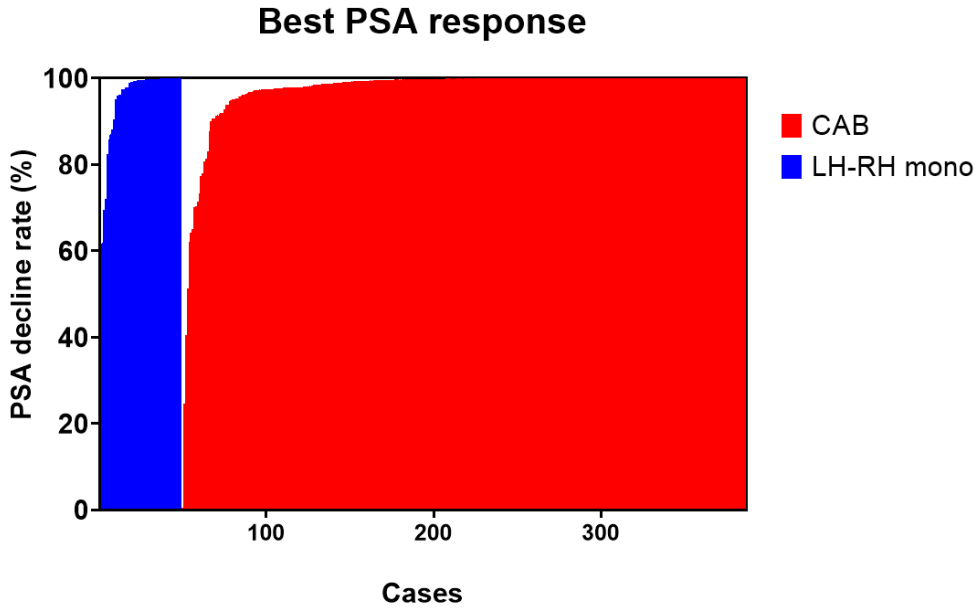
Review Comments

Comment 1: This is a retrospective study that can be valuable by providing a view on current practice. However, the manuscript's message is weakened by the lack of clarifying information.
Testosterone monitoring, how many patients in each group had a testosterone assay. Among those assessed, what were the actual rates of effective castration.

Reply 1: Thank you for the instructive comment. We agree with the suggestion. Unfortunately, we have not corrected the data on testosterone levels. We described this issue in the limitation part. Please see page 16, line 270.
Changes in the text: Page 16, line 270, lack of data of testosterone levels after hormonal therapy,

Comment 2: PSA monitoring: compare the waterfall plots of best PSA responses between the two groups.

Reply 2: Thank you for the instructive comment. We conducted an additional analysis of PSA best response rate. Please see Page 10, line 160-162, Page 12, line 195-196.
Changes in the text: Page 10, line 160-162, In addition, the PSA best response rate was assessed. Patients with missing PSA nadir data were excluded from the PSA best response rate analysis. PSA best response rate was defined as (iPSA – nadir PSA) / (iPSA). PSA best response rate was defined as (iPSA – nadir PSA) / (iPSA).
Page 12, line 195-196 There is no significant difference in PSA best response rate (median: 99.5% vs. 99.8%, p = 0.15, respectively, Fig.S1).
Supplementary figure 1.



Comment 3: Survival analysis, specify
1) the time of origin (=date of diagnosis of prostate cancer? diagnosis of metastases? date of start androgen deprivation)
2) the time of event and define what is/are the event/s.

Reply 3: Thank you for the instructive comments and we apologize for confusion. We described the definition of survival analysis. Please see page 10, line 156-159.
Changes in the text: page 10, line 156-159, We analyzed overall survival (OS), which was defined as the time from start of ADT until all-cause death or last patient contact. Cancer-specific survival (CSS) was defined as the time from start of ADT until cancer death or last patient contact. CRPC-FS was defined as the time from start of ADT until progression toward CRPC.

Comment 4: Initial PSA, clarify PSA at the time of cancer diagnosis, at metastasis?

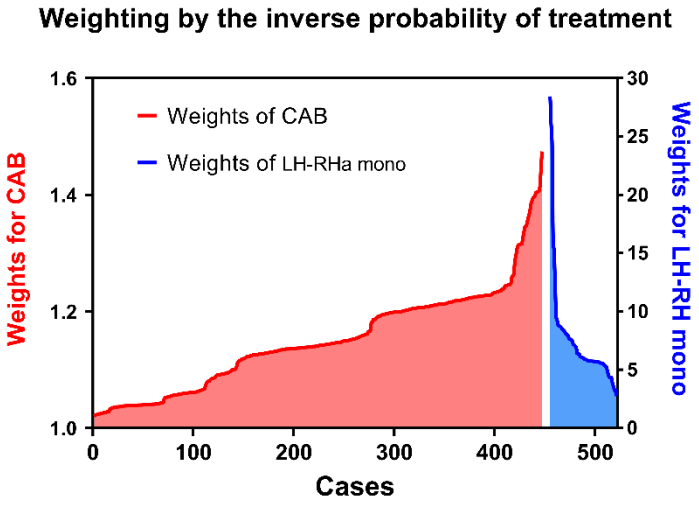
Reply 4: Thank you for the instructive comments and we apologize for confusion. We described the definition of initial PSA in the Methods part. Please see page 8, line 126.
Changes in the text: page 8, line 126, initial prostate-specific antigen (iPSA) levels at the time of cancer diagnosis

Comment 5: Inverse probability of treatment weighting (IPTW): Justify the choice of variables used. Provide the output of the statistical verifications.

Reply 5: Thank you for important comments. The propensity score is defined as a probability of treatment selection in each individual on observed baseline covariates. The propensity score-based IPTW method creates a pseudo-population and removes

the background unbalances between the two groups, and obtain unbiased estimates of average treatment effects. IPTW-adjusted Cox regression analysis includes 3 steps: 1) propensity score calculation for treatment, 2) calculation of inverse-probability weighting, and 3) Cox regression analysis with the robust method.
It is difficult to demonstrate the statistically appropriateness of the choice of variables for calculating the propensity score. The propensity score is the aggregation of multiple background factors that could be bias into a single variable.
We added an analysis of the weight for treatment (Fig. S3) to confirm the validity of our IPTW analysis. In the LH-RH mono group, the weight per case is greater due to the small number of cases. The limitation of our IPTW method is the over-weighted effects of minority groups that are far from the center of the patient background. We described this point in discussion parts.

Changes in the text: page 16, line 268-269, over-weighted effects of minority groups that are far from the center of the patient background of the IPTW method (Fig.S4), Supplementary figure 4.



Comment 6: Extent of disease and CHAARTED high-volume are undefined.

Reply 6: Thank you for the instructive comments and we apologize for confusion. We described the definitions of extents of disease and CHAARTED high-volume disease. Please see Page 8, line 127-133.

Changes in the text: page 8, line 127-133, EOD were used to evaluate the extent of bone metastasis, the grades were EOD 0, normal or abnormal due to benign bone disease; EOD 1, <6 metastases; EOD 2, 6–20 metastases; EOD 3, >20 metastases but not a superscan; and EOD 4, superscan. CHAARTED high-volume disease was defined as the presence of visceral metastases or bone metastasis ≥4 with at least one bone metastasis must be present outside the vertebral bodies and pelvis in accordance with the CHAARTED study (16).