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Platinum Priority – Editorial

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Further Randomized Data Confirming Minimal Benefit from the Addition of Hormone Therapy to Postoperative Radiotherapy

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Parker and colleagues [1] are to be congratulated on the important results published in this issue of *European Urology* from the three-way randomized arms from the RADICALS-HD trial on the use and duration of hormone therapy (HT) with postoperative radiotherapy. This component of the platform trial randomized 492 men after prostatectomy to either 0 mo, 6 mo, or 24 mo of HT. At median follow-up of 9.0 yr, there were no significant differences in freedom from distant metastasis (FFDM), metastasis-free survival (MFS), or overall survival (OS) between the groups. While at first glance one might assume that the trial was simply underpowered, closer examination reveals that these results are highly consistent with those from NRG/RTOG 9601, NRG/RTOG 0534, GETUG-AFU-16, and the two-way randomized trials from RADICALS-HD [2–6].

Figure 1A compares results for the absolute difference in OS with addition of HT across trials in intact disease with definitive radiotherapy in comparison to postprostatectomy radiotherapy, as well as the landmark MARCAP meta-analysis results for localized disease [7]. Addition of HT to definitive radiotherapy for localized disease improved OS by ~7–8%, depending on the inclusion criteria of EORTC 22863, a trial of 0 versus 36 mo of HT. This translates into a number needed to treat (NTT) of ~13–14 to prevent one death at 10 yr. By contrast, assessment of all postoperative trials of HT use, with the exclusion of the prespecified prostate-specific antigen (PSA) stratum of >1.5 ng/ml in NRG/RTOG 9601 of very late salvage radiotherapy, reveals that no trial has reported 8–12-yr OS differences greater than ~1%, with multiple trials having a numerically nonsignificant detriment in OS. If one were to use an NNT threshold of 33, or a 3% absolute improvement in OS from addition of HT, it is clear that this is consistently not achieved in postoperative patients.

Similarly, Figure 1B compares results for the absolute difference in OS from the prolongation of HT across trials in intact disease with definitive radiotherapy versus post-prostatectomy radiotherapy, as well as the landmark MARCAP meta-analysis results for localized disease [7]. The MARCAP meta-analysis estimated that prolongation of short-term to long-term HT in localized disease improved OS by 5.5%, or an NNT of 18. By contrast, in the two RADICALS-HD trials that compared short- versus long-term HT with postoperative radiotherapy, the 10-yr OS benefit from HT prolongation was <3% and did not cross an NNT threshold of 33. Furthermore, neither the RADICALS-HD two-way or three-way trial reached statistical significance for an improvement in OS.

Why are the results for addition of HT to radiotherapy so different between intact and postoperative disease? I present two hypotheses for consideration. First, unlike localized prostate cancer, for which radiotherapy dose escalation has demonstrated clear improvements in biochemical-based endpoints, even in low-grade cancers, postoperative prostate cancer did not exhibit the same benefits in postoperative radiotherapy trials that escalated the biologically effective dose (SAKK 09/10, PKUFH trial, NRG GU003). This may simply be because of the substantial difference in the volume of cancer cells between intact and postprostatectomy disease, and thus the exponentially lower log cell-kill required. This is consistent with the lack of clear OS benefit from addition of HT to postoperative

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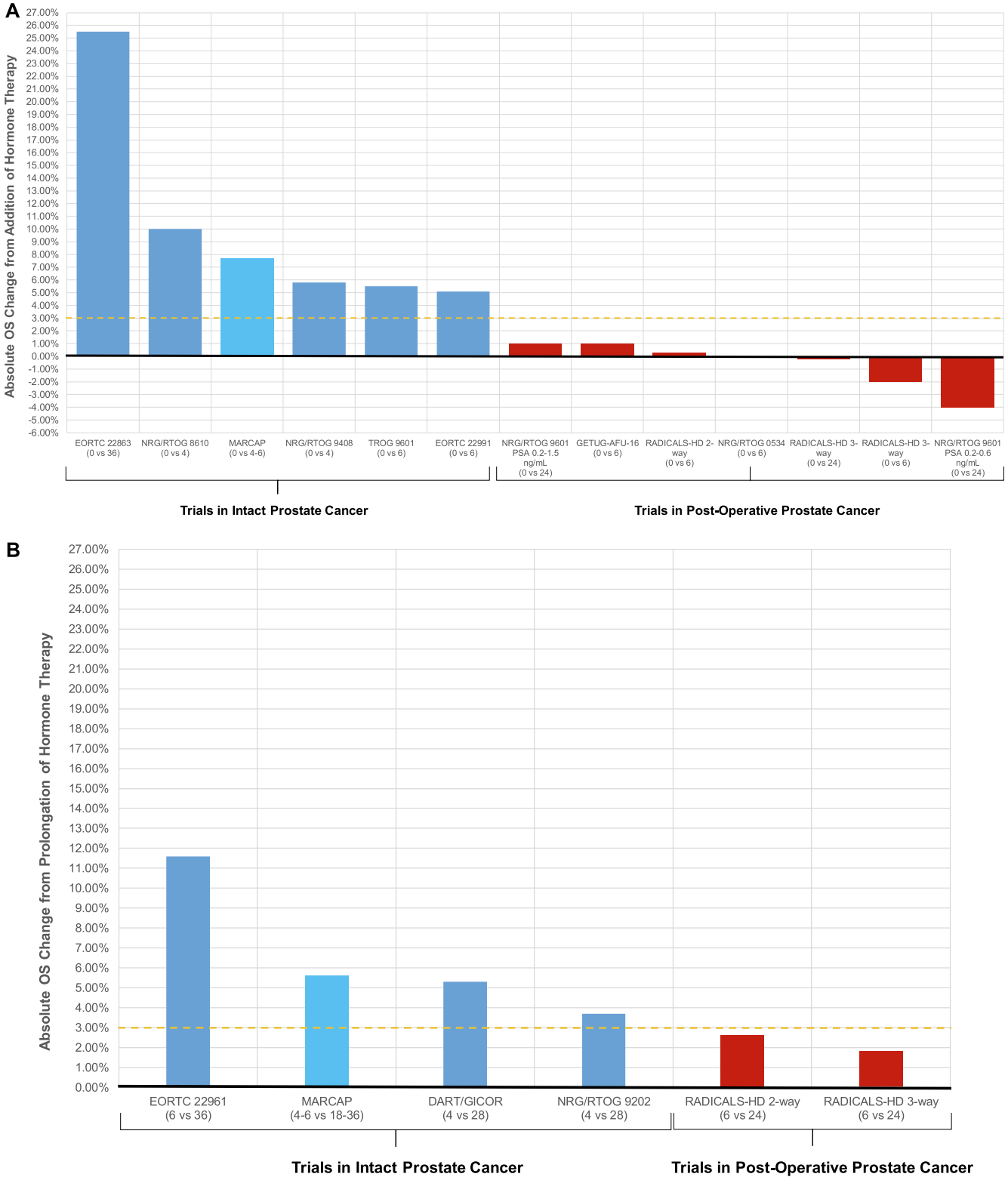

Fig. 1 – Comparison of the absolute overall survival benefit for intact versus postoperative prostate cancer from (A) addition of hormone therapy to radiotherapy and (B) prolongation of hormone therapy (from 4–6 mo to 24–36 mo) with radiotherapy. PSA = prostate-specific antigen.

radiotherapy except for patients with high PSA, who have a high probability of already harboring nodal or distant metastatic disease. HT improves outcomes with radiotherapy in part by inhibiting androgen receptor–regulated DNA repair, and thus functionally radiosensitizing the tumor [8]. This does not appear to be required after prostatectomy with the current doses of radiotherapy used and the low cellularity of microscopic disease.

Second, is the lack of either short-term or long-term HT with postprostatectomy radiotherapy truly demonstrating

greater "cures" or a flattening of the FFDM curves. As shown by Parker et al [1] in both the two-way and three-way RADICALS-HD trials, use and prolongation of HT had no effect on flattening of the FFDM curve to create a tail representing greater "cure". Rather, it appears that early and longer HT use suppresses PSA and delays biochemical progression, and thus subsequent salvage HT in the subset of patients who require it. Thus, administration of 24 mo of HT appears to largely create a transient sense of reassurance that you are improving outcomes, when in reality these patients ultimately experience similar rates of metastasis, albeit delayed, and most men are overtreated and will have similar OS to those not receiving concurrent HT.

In summary, Parker et al [1] and the RADICALS teams are to be congratulated again for reporting these results, which ultimately should reassure providers that omission of HT or use of a shorter HT duration is unlikely to compromise long-term survival endpoints. Future work using transcriptomic and digital pathology–based biomarkers are needed to personalize the use and duration of HT after prostatectomy.

Conflicts of interest: The author has received personal fees from Astellas, AstraZeneca, Bayer, Boston Scientific, Janssen, Novartis, and Pfizer outside the scope of this manuscript.

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