original reports

Prostate Radiotherapy With Adjuvant Androgen Deprivation Therapy (ADT) Improves Metastasis-Free Survival Compared to Neoadjuvant ADT: An Individual Patient Meta-Analysis

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abstract

PURPOSE There remains a lack of clarity regarding the influence of sequencing of androgen deprivation therapy (ADT) and radiotherapy (RT) on outcomes in prostate cancer (PCa). Herein, we evaluate the optimal sequencing of ADT with prostate-directed RT in localized PCa.

METHODS MEDLINE (1966-2018), Embase (1982-2018), ClinicalTrials.gov, and conference proceedings (1990-2018) were searched to identify randomized trials evaluating the sequencing, but not duration, of ADT with RT. Two randomized phase III trials were identified, and individual patient data were obtained: Ottawa 0101 and NRG Oncology's Radiation Therapy Oncology Group 9413. Ottawa 0101 randomly assigned patients to neoadjuvant or concurrent versus concurrent or adjuvant short-term ADT. Radiation Therapy Oncology Group 9413, a 2 × 2 factorial trial, included a random assignment of neoadjuvant or concurrent versus adjuvant short-term ADT. The neoadjuvant or concurrent ADT arms of both trials were combined into the neoadjuvant group, and the arms receiving adjuvant ADT were combined into the adjuvant group. The primary end point of this meta-analysis was progression-free survival (PFS).

RESULTS The median follow-up was 14.9 years. Overall, 1,065 patients were included (531 neoadjuvant and 534 adjuvant). PFS was significantly improved in the adjuvant group (15-year PFS, 29% *v* 36%, hazard ratio [HR], 1.25 [95% CI, 1.07 to 1.47], $P = .01$). Biochemical failure (subdistribution HR [sHR], 1.37 [95% CI, 1.12 to 1.68], $P = .002$), distant metastasis (sHR, 1.40 [95% CI, 1.00 to 1.95], $P = .04$), and metastasis-free survival (HR, 1.17 [95% CI, 1.00 to 1.37], $P = .050$) were all significantly improved in the adjuvant group. There were no differences in late grade ≥ 3 gastrointestinal (2% *v* 3%, $P = .33$) or genitourinary toxicity (5% *v* 5%, $P = .76$) between groups.

CONCLUSION The sequencing of ADT with prostate-directed RT has significant association with long-term PFS and MFS in localized PCa. Our findings favor use of an adjuvant over a neoadjuvant approach, without any increase in long-term toxicity.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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In most cancer types, there is level 1 evidence for the benefit of the addition of systemic therapy to radiotherapy (RT).[1-5] Furthermore, randomized trials have demonstrated that the sequencing of systemic therapy and RT is of importance to optimize survival outcomes.[1,6] In localized and recurrent prostate cancer (PCa), over 20 randomized trials have established the important role of combining various durations of androgen deprivation therapy (ADT) with RT. However, these trials have almost exclusively focused on the use and duration of ADT rather than the sequencing of ADT with RT.[7-19]

The sequencing strategy of ADT and RT varies internationally and among the research cooperative groups. For example, NRG Oncology's Radiation Therapy Oncology Group (RTOG) trials often used a 2-month neoadjuvant component while the Canadian and Australian trialist groups commonly used longer durations of neoadjuvant ADT. By contrast, the European Organization for Research and Treatment of

CONTEXT

Key Objective

To compare the long-term outcomes of men with localized prostate cancer receiving radiotherapy (RT) and neoadjuvant versus adjuvant short-term hormone therapy.

Knowledge Generated

After a median follow-up of approximately 15 years, we demonstrate using individual patient data from two randomized trials that men treated with adjuvant hormone therapy with prostate-directed RT had improved biochemical control and metastasis-free survival compared to a neoadjuvant or concurrent approach of equal duration. There were very low rates of late gastrointestinal or genitourinary grade 3 or higher toxicity, and no differences were found in toxicity based on hormone therapy timing.

Relevance

Delaying the start of RT by use of a neoadjuvant component of hormone therapy did not provide an advantage in tumor control or late toxicity based on our pooled randomized analysis but may have inferior clinically meaningful outcomes than use of an adjuvant sequence with prostate-directed RT.

Cancer (EORTC) group often started ADT concomitantly with RT without a neoadjuvant component. Although these studies provide us clarity on the optimal duration of ADT, optimal sequencing approach of ADT with RT remains unclear.

Early preclinical studies by Zietman et al[20] used a mouse-derived breast tumor model and demonstrated superior results with neoadjuvant compared with adjuvant surgical castration. However, the neoadjuvant group was functionally neoadjuvant, concurrent, and adjuvant, given this was surgical castration. A single-institution retrospective analysis (N = 515 patients) was unable to identify a difference in any oncologic outcome between the sequencing of neoadjuvant versus adjuvant ADT with RT.[21] Only two randomized trials have investigated the impact of sequencing of ADT with RT without altering the total duration of ADT: the Ottawa 0101 randomized phase III trial, and the NRG Oncology's RTOG 9413 trial (Protocol, online only), a 2 × 2 factorial randomized phase III trial.[22,23] Each of these two trials have individually demonstrated the possibility of a superior outcome with an adjuvant versus a neoadjuvant component of ADT when combined with prostate-directed RT, but neither was conclusive. Therefore, we performed the first individual patient-level meta-analysis of these two phase III randomized controlled studies that investigated the optimal sequencing of ADT with prostate-directed RT.

METHODS

A systematic literature search was performed using MEDLINE (1966-2018), Embase (1982-2018), trial registries (Cochrane Central Register of Controlled Trials and ClinicalTrials.gov), and major urology and oncology conference proceedings (1990-2018) to retrieve studies that evaluated the optimal sequencing of definitive RT with ADT in men with localized PCa. Controlled vocabulary was leveraged for studies involving humans using the following terms: randomized AND prostate AND (androgen deprivation OR hormone therapy) AND (radiotherapy OR radiation) AND (neoadjuvant OR adjuvant) NOT prostatectomy. The search was conducted on January 2, 2020. Two randomized trials were identified and were included in this meta-analysis (Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data can be found in the Appendix Fig A1 [online only]). After institutional review board and data-sharing agreements were approved, individual patient data were collected from the NRG Oncology's RTOG 9413 trial[23] (Protocol) and Ottawa 0101 randomized phase III trial.[22]

Study Cohorts

NRG Oncology's RTOG 9413. The NRG Oncology's RTOG 9413 study (Protocol) was designed as a 2 × 2 factorial phase III randomized study with hormonal sequencing as one stratification factor and RT field size as the other factor. The primary end point related to ADT sequencing was whether neoadjuvant ADT improved progression-free survival (PFS) compared to adjuvant ADT. Eligible patients had histologically confirmed, clinically localized prostate adenocarcinoma with an estimated risk of lymph node involvement > 15% and a Karnofsky performance status > 70. Patients were randomly assigned (1:1:1:1) by permuted block random assignment to receive either neoadjuvant and concurrent ADT 2 months before and 2 months during prostate-directed RT versus prostate-directed RT followed by 4 months of adjuvant ADT. This was done similarly for the whole pelvis RT arms. Random assignment was stratified by clinical tumor (T) stage, Gleason score, and prostate-specific antigen (PSA) concentration. ADT was combined androgen suppression, consisting of goserelin acetate 3.6 mg once a month subcutaneously or leuprolide acetate 7.5 mg once a month

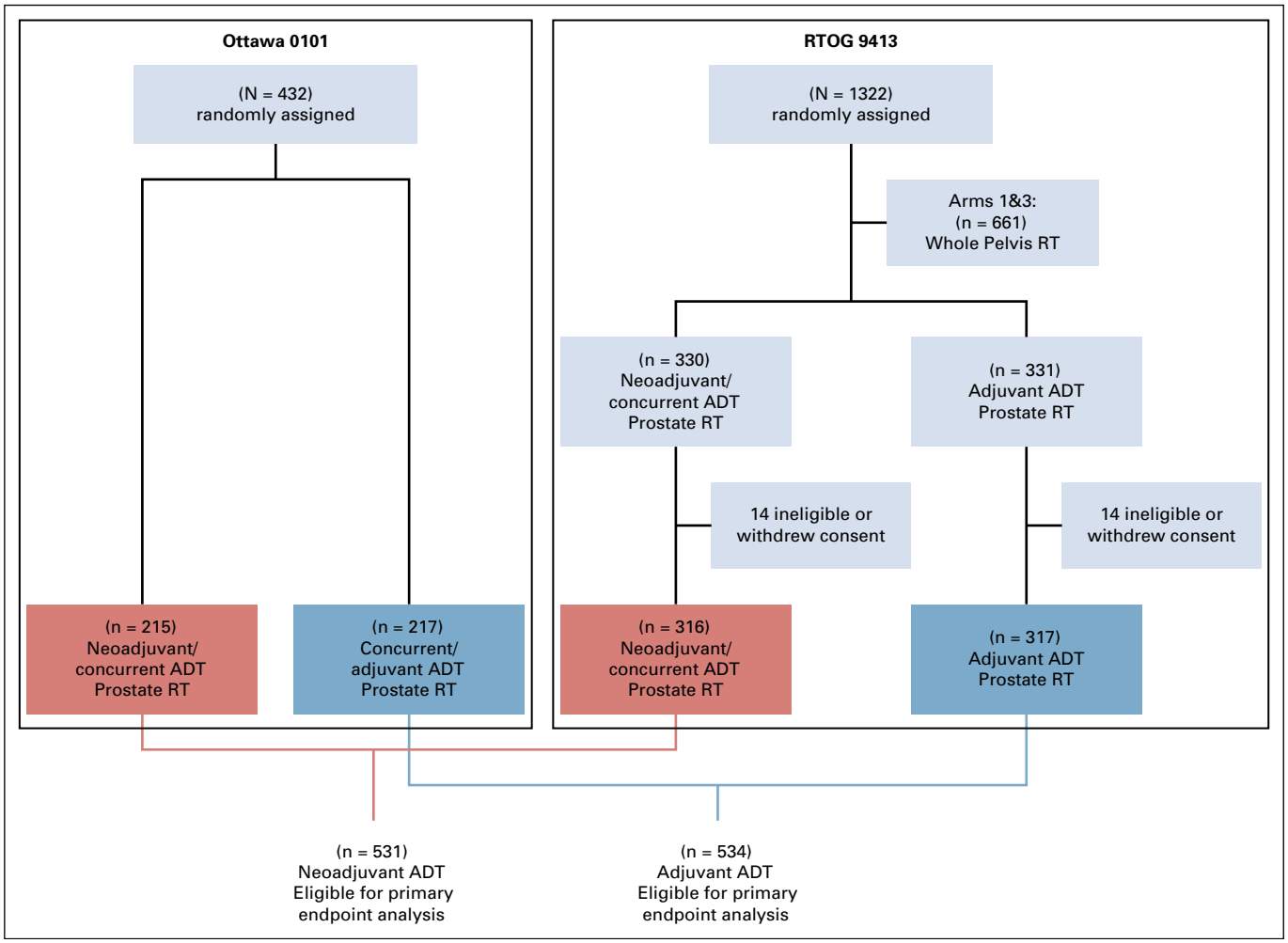

FIG 1. Consolidated Standards of Reporting Trials (CONSORT) Diagram. ADT, androgen deprivation therapy; RT, radiotherapy.

intramuscularly, and flutamide 250 mg orally three times a daily for 4 months. The primary end point of PFS was defined as the time from random assignment to the first occurrence of local progression, regional or nodal failure, distant metastasis (DM), biochemical failure (BF) (Phoenix definition), or death from any cause.

Only the prostate-directed RT randomized arms were used in this study to avoid potential interactions of field size and ADT sequencing, and to harmonize with the Ottawa 0101 trial, which used prostate-directed RT. Between April 1, 1995, and June 1, 1999, a total of 1,322 patients were enrolled from 53 centers and randomly assigned to one of the four treatment groups.

Ottawa 0101. The Ottawa 0101 was an open-label, parallel, two-arm phase III randomized trial. The primary end point was biochemical relapse-free survival (defined as time since random assignment to either biochemical recurrence as per Phoenix criteria, commencement of salvage ADT even in the absence of per-protocol progression, or clinical progression). All patients received a total 6 months of ADT. Patients in arm 1 received 4 months of neoadjuvant ADT followed by RT concurrently with 2 months of ADT. In arm 2, patients received ADT concomitantly with RT for the first 2 months followed by 4 months of adjuvant ADT. Eligible patients had histologically confirmed prostate adenocarcinoma with a Gleason score ≤ 7, clinical stage T1b to T3a, and PSA < 30 ng/mL. Patients with low-risk PCa were excluded. ADT comprised bicalutamide 50 mg orally once a day plus 10.8 mg goserelin subcutaneously once starting 7 days after bicalutamide, and again with a second injection administered 3 months later. Between July 12, 2002, and March 28, 2012, a total of 438 patients were enrolled from two centers and randomly assigned to one of the two treatment groups.

In this meta-analysis, the neoadjuvant and concurrent arms of both trials were combined into the neoadjuvant group, and the concurrent and adjuvant (Ottawa 0101) and

End Point	Neoadjuvant Incidence/N	Adjuvant Incidence/N	15-yr Absolute Benefit of Adjuvant ADT (%, CI 95%)	15-yr RMST Benefit of Adjuvant ADT (Months, CI 95%)	HR (95%)	*P* value
Progression-free survival	316/531	292/534	7.4 (−0.1, 14.8)	10.8 (2.7, 18.8)	1.25 (1.07, 1.47)	.01
Biochemical failure	214/531	168/534	10.1 (3.8, 16.3)	12.4 (3.7, 21.1)	1.37 (1.12, 1.68)	.002
Distant metastasis	82/531	60/534	5.3 (0.5, 10.1)	2.9 (−2.6, 8.4)	1.40 (1.00, 1.95)	.04
Metastasis-free survival	324/531	298/534	7.2 (0.3, 14.1)	3.9 (−3.1, 10.8)	1.17 (1.00, 1.37)	.050
Prostate cancer-specific mortality	91/531	73/534	5.8 (0.5, 11.0)	3.5 (−1.6, 8.6)	1.29 (0.95, 1.75)	.10
Overall survival	307/531	291/534	5.4 (−1.6, 12.3)	2.7 (−4.0, 9.3)	1.11 (0.95, 1.30)	.20

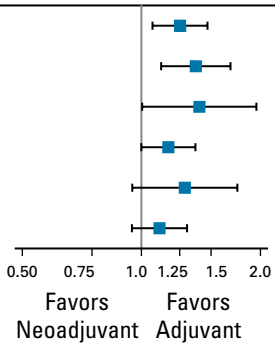

FIG 2. Forest plot of oncologic outcomes comparing neoadjuvant versus adjuvant ADT. ADT, androgen deprivation therapy; HR, hazard ratio; RMST, restricted mean survival time.

adjuvant arm (RTOG 9413; Protocol) were combined into the adjuvant group.

End Points

The primary end point of this analysis was PFS, defined as the time from random assignment to the first occurrence of local, regional, or nodal failure, DM, BF (Phoenix definition), or death from any cause. Secondary end points included metastasis-free survival (MFS) defined as time since random assignment until metastasis or death, overall survival (OS), and the cumulative incidence of BF, DM, and PCa-specific mortality (PCSM; death from PCa as the event). Patients who were event-free were censored on the last date of follow-up or on the date of last follow-up with known biochemical or clinical status. Late toxicity was analyzed as reported by each study and was categorized into genitourinary (bladder) and gastrointestinal (bowel) toxicity. Rates of severe toxicity in each category, defined as grade 3-5, were estimated for the two treatment groups.

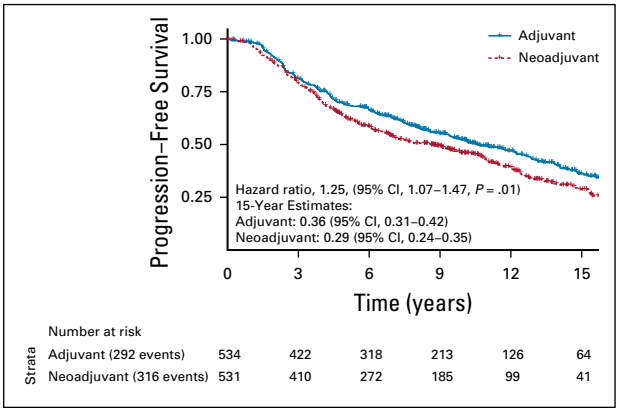

FIG 3. Kaplan-Meier of the primary end point of progression-free survival comparing adjuvant versus neoadjuvant ADT with RT. ADT, androgen deprivation therapy; HR, hazard ratio; RT, radiotherapy.

Statistical Analysis

An a priori statistical plan was created prior to data pooling and analysis. Baseline characteristics were compared by treatment group using the Mann-Whitney-Wilcoxon test for age and the χ^2 test for all other baseline characteristics. Treatment effects on PFS, MFS, and OS were reported using the hazard ratio (HR) with 95% CIs from Cox regression models along with absolute differences in Kaplan-Meier event probability estimates.[24,25] The Grambsch-Therneau test was applied to identify violation of proportionality assumption of the Cox regression models. For cumulative incidence of BF, DM, and PCSM, the subdistribution HRs (sHR) with 95% CI were reported from Fine-Gray's competing risk regression models along with cumulative incidence of events. Death from any cause served as competing events for BF and DM, and deaths not resulting from PCa were considered competing events for PCSM.[26-29] HRs were defined such that HR $>$ 1 favored the adjuvant group compared with the neoadjuvant group. Formal interaction tests between treatment and clinicopathologic covariables and the National Comprehensive Cancer Network risk group were performed.

For each treatment group, we also estimated 15-year restricted mean survival time (RMST) for OS, MFS, and PFS, and 15-year restricted mean time lost (RMTL) for DM, BF, and PCSM to account for competing risk of death. RMST was determined from the Kaplan-Meier estimate of the survival function, whereas RMTL was determined from the estimated cumulative incidence function. The treatment effect on each end point was assessed by taking the difference in RMST estimates between adjuvant and neoadjuvant groups; however, for RMTL, the direction was reversed to keep the

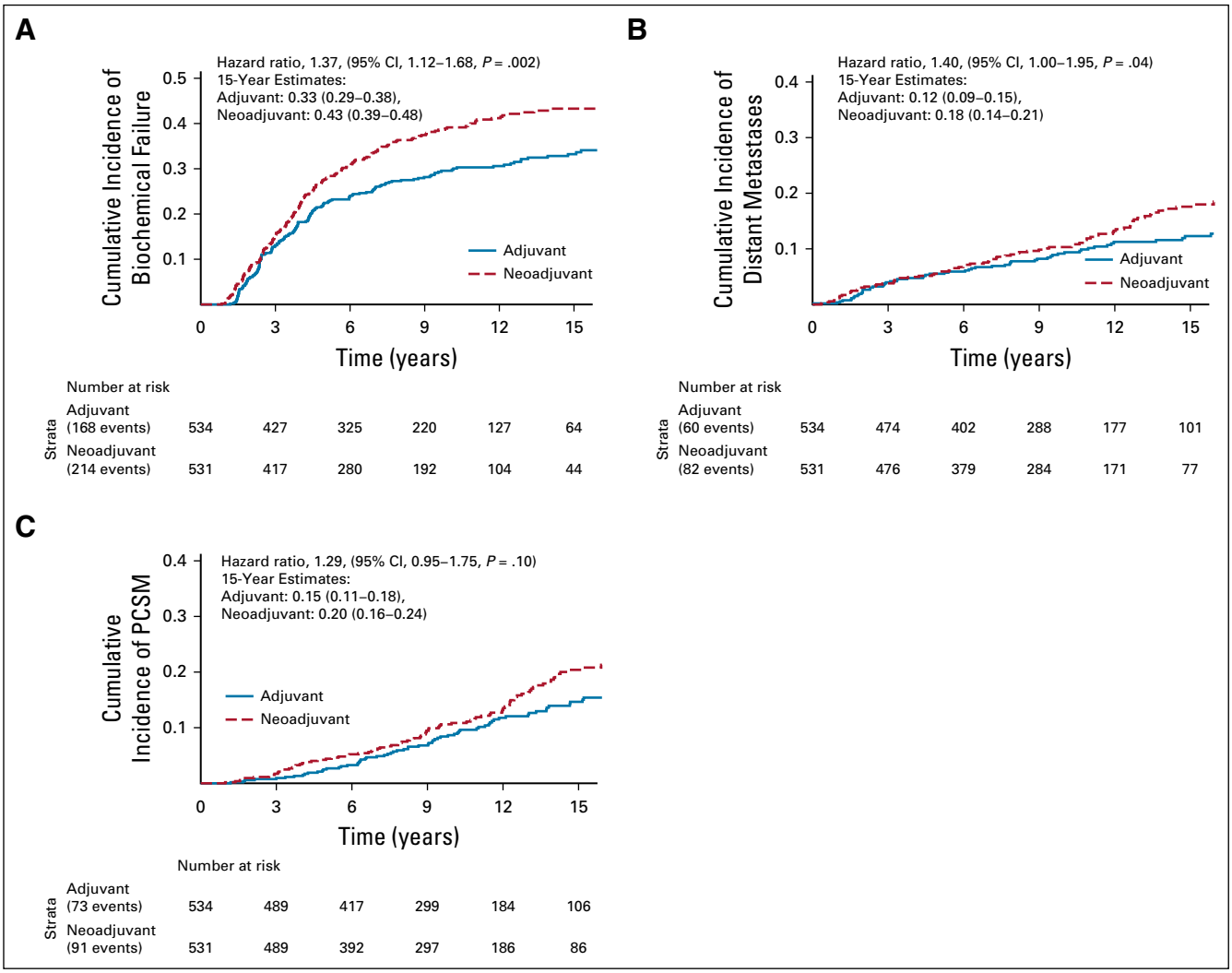

FIG 4. Comparison of adjuvant versus neoadjuvant ADT with RT. (A) Cumulative incidence of biochemical failure, (B) distant metastasis, and (C) prostate cancer–specific mortality. ADT, androgen deprivation therapy; RT, radiotherapy.

interpretation consistent. Analyses were repeated after adjustment for trial enrollment (RTOG 9413 [Protocol] *v* Ottawa 0101) to account for any potential systematic differences between trials. Grade 3-5 late toxicity events were summarized for both treatment groups. The effect of treatment arms was assessed using odds ratios, and the 95% CIs and *P* values were obtained using the exact test with mid-*P* adjustment. Analyses were performed using R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P < .05$ was deemed statistically significant.

RESULTS

The median follow-up was 14.9 years, and a total of 1,065 patients were included (531 in the neoadjuvant ADT group and 534 in the adjuvant ADT group; Fig 1). All baseline characteristics were well balanced (Table 1). The median age was 70 years (interquartile range [IQR], 65-74); 58.1% had a Gleason score of 7 and 16.9% had a Gleason score of 8-10. Overall, 19.6% had clinical T3 and T4 disease, and the median PSA was 14.1 ng/mL (IQR, 8.30-26.50 ng/mL).

In the pooled cohort, the primary end point of PFS was significantly improved in the adjuvant group compared with the neoadjuvant group. Up to a 15-year truncation point, RMST for progression was improved with adjuvant ADT by 10.8 months (95% CI, 2.7 to 18.8) (Fig 2). Fifteen-year PFS rates for neoadjuvant and adjuvant groups were 29% and 36%, respectively (Fig 3). On the Cox regression, the HR for the neoadjuvant group was 1.25 (95% CI, 1.07 to 1.47, $P = .01$). Similarly, the cumulative incidences of BF (15-year incidence rates, 43% *v* 33%, sHR for neoadjuvant group, 1.37 (95% CI, 1.12 to 1.68, $P = .002$); Fig 4A) and DM (15-year incidence rates, 18% *v* 12%, sHR for neoadjuvant

TABLE 1. Baseline Characteristics

Variable	All Patients	Adjuvant ADT	Neoadjuvant ADT	*P*
N	1,065	534	531	
Age (y)				.23
Median (IQR)	70 (65, 74)	70 (65, 74)	70 (66, 74)	
Gleason score				.67
< 7	266 (25.0)	135 (25.3)	131 (24.7)	
7	619 (58.1)	304 (56.9)	315 (59.3)	
8-10	180 (16.9)	95 (17.8)	85 (16.0)	
T stage				.95
T1/T2a	448 (42.1)	223 (41.8)	225 (42.4)	
T2b/T2c	408 (38.3)	207 (38.8)	201 (37.9)	
T3/T4	209 (19.6)	104 (19.5)	105 (19.8)	
PSA (ng/mL)				.33
Median (IQR)	14.10 (8.30, 26.50)	13.77 (8.10, 26.50)	14.40 (8.62, 26.14)	
0-10	376 (35.3)	197 (36.9)	179 (33.7)	
11-20	310 (29.1)	145 (27.2)	165 (31.1)	
> 20	379 (35.6)	192 (36.0)	187 (35.2)	

Abbreviations: ADT, androgen deprivation therapy; IQR, interquartile range; PSA, prostate-specific antigen.

group, 1.40 [95% CI, 1.00 to 1.95], $P = .04$; Fig 4B) were significantly lower in the adjuvant group compared with the neoadjuvant group. The adjuvant group was associated with significantly superior MFS relative to the neoadjuvant group (HR for neoadjuvant group, 1.17 [95% CI, 1.00 to 1.37], $P = .050$).

Adjuvant ADT yielded lower PCSM (15-year incidence rates, 20% *v* 15%, sHR for neoadjuvant group, 1.29 (95% CI, 0.95 to 1.75, $P = .10$; Fig 4C), but this did not reach the level of statistical significance. In men with high-risk PCa, the effect size of benefit from adjuvant ADT was larger for PCSM (sHR, 1.39 [95% CI, 1.00 to 1.93, $P = .053$; Appendix Fig A2), but remained statistically nonsignificant. There was no statistical evidence of a treatment interaction by the National Comprehensive Cancer Network risk group ($P = .32$). There was also no significant difference in OS between the groups (15-year rates, 34% *v* 39% for the neoadjuvant and adjuvant groups, respectively; HR for the neoadjuvant group, 1.11 [95% CI, 0.95 to 1.30], $P = .20$).

Given trial-level differences (eg, years of enrollment, ADT duration, country of primary enrollment, etc), analyses for all oncologic outcomes were repeated after adjustment for clinical trial. As shown in the Appendix Fig A3, the outcomes remained effectively unchanged, with adjuvant ADT having superior outcomes for all end points.

There were no significant differences in either late grade 3-5 gastrointestinal (2% *v* 3%, $P = .33$) or genitourinary toxicity (5% *v* 5%, $P = .76$) between the neoadjuvant versus adjuvant groups, respectively.

DISCUSSION

The current individual patient-level meta-analysis of two randomized phase III trials with long-term follow-up demonstrated significant improvements in several clinically meaningful oncologic outcomes with short-term adjuvant ADT relative to neoadjuvant ADT when used in conjunction with prostate-directed RT. Additionally, overall rates of late grade 3-5 toxicities were low, and we did not find any significant difference in the incidence of severe gastrointestinal or genitourinary toxicities between the two groups. When the trials are viewed individually, there were trends noted for improved BF and PFS in the RTOG 9413 (Protocol) and Ottawa 0101 trials. This meta-analysis with a larger patient population consolidates the findings of the above trials and demonstrates a significant reduction in the relative incidence of DM with improved MFS, which is a unique and important observation.

Several randomized trials have investigated the utility of prolongation of the neoadjuvant component. The Quebec L-101 (N = 120),[12] RTOG 9910 (N = 1,579),[19] Canadian Multicenter Trial (N = 378),[10] and Irish Clinical Oncology Research Group 97-01 (N = 261)[18] randomized trials failed to demonstrate any improvement in oncologic outcomes from the prolongation of the course of neoadjuvant ADT. By contrast, the use and increased duration of adjuvant ADT have consistently resulted in meaningful improvements in MFS, PCSM, and/or OS (ie, TROG RADAR and DART trials 01/05, RTOG 9202, and EORTC 22961).[8,9,14,30] These results reflect that an increased duration of ADT might not be the driver of improved oncologic outcomes, and that the

timing of ADT in relation to RT is important to optimize outcome in localized PCa.

In this context, the interpretation of a prior pooled analysis of three randomized trials merits reconsideration.[11] This analysis, by D'Amico et al,[11] included two trials of predominately neoadjuvant ADT with 1 month of concurrent ADT (a total duration of 3-4 months), and compared this group with patients who received 4 months of neoadjuvant and concurrent ADT plus 2 months of adjuvant ADT (a total of 6 months). They demonstrated that 6 months of ADT conferred a large improvement in PCSM (HR, 0.55; 95% CI, 0.36 to 0.82) compared with the shorter duration of ADT. The authors attributed the improvement to increased duration of ADT rather than the difference in sequencing. However, as previously noted, multiple trials that compared 3-4 months of ADT with an increased duration of neoadjuvant ADT (a total duration $>$ 6 months) failed to demonstrate any difference in oncologic outcomes.[10,19] Thus, perhaps the sequencing of ADT was the true reason for the improvement of outcomes.

Neoadjuvant and concurrent ADT effectively provide a short period of adjuvant ADT due to prolonged testosterone suppression. This begs the question if trials like RTOG 9408, which prescribed neoadjuvant and concurrent ADT, provided most of the benefit from the short duration of residual adjuvant testosterone suppression rather than the neoadjuvant and concurrent active drug delivery. Similarly, the TROG 96.01 trial of 0 versus 3 months versus 6 months ADT (no adjuvant ADT given) demonstrated that the primary end point of PCSM was only significantly improved once 6 months of ADT was given, potentially due to prolonged adjuvant testosterone suppression. This theory was effectively examined in the Princess Margaret Hospital 9907 (N = 252) randomized trial of men with intermediate-risk disease, in which men were randomly assigned positive or negative antiandrogen therapy rather than ADT. Thus, there was no adjuvant testosterone suppression.[31] This trial gave 150 mg of bicalutamide once a day for 5 months in the neoadjuvant and concurrent phase with RT, and showed no improvement in any oncologic end point, or even in biochemical control, from neoadjuvant and concurrent antiandrogen therapy. All these findings taken together point toward the importance of adjuvant ADT when used in conjunction with RT in localized PCa.

Several factors may account for the sequence-dependent interaction between ADT and RT in PCa. These include an inhibitory action of adjuvant ADT on enhanced ligand-dependent activation of the androgen receptors (ARs), which are found to be overexpressed after RT.[32] Moreover, due to the prolonged natural history of RT induced cell death in PCa, which occurs over months to years to achieve maximal PSA nadir, continued adjuvant inhibition of AR-regulated DNA repair genes may be critical for optimal outcomes. Additionally, neoadjuvant ADT might have competing benefits from reduction in tumor hypoxia that might enhance sensitivity to RT and a decrease in the proliferation of cancer cells, resulting in reduced radiosensitivity.[33] This latter point formed the basis of the original hypothesis to test ADT sequence in RTOG 9413, as stated in the original RTOG 9413 Protocol.

Our meta-analysis used individual patient data from two trials specifically conceived and conducted to test the hypothesis of our study. Each group in our study included all patients assigned to the relevant groups of the constituent trials to harmonize with consistent prostate-directed target volume for RT delivery. Nonetheless, we acknowledge potential limitations of our meta-analysis. Extensive effort was made to ensure these were the only two phase III randomized trials to have assessed the question of ADT sequencing (with a constant duration of ADT) with RT, but potential limitations exist with any search strategy. Patients allocated to the whole-pelvic RT arm of the RTOG 9413 study (Protocol) were not included in this meta-analysis to harmonize the mode of RT delivery with the Ottawa 0101 trial. There was a hypothesis that generated post hoc, unplanned interaction in RTOG 9413 (Protocol), identified between RT field size and ADT sequencing. However, as stated in the RTOG 9413 Protocol, there was no intention of testing for a treatment interaction given that "these factors are not expected to show any statistical interaction with treatment" (Protocol). Given that the Ottawa trial did not include patients treated with nodal RT, we are unable to validate this potential interaction. There were systematic differences in the two trials in our study (duration of ADT, exact timing of ADT in relation to RT, years of enrollment, formulation of ADT used, etc). However, our findings remained effectively unchanged when adjusting for trial enrollment. Given that the RTOG 9413 trial (Protocol) enrolled patients with more aggressive disease than the Ottawa 0101 trial, our ability to soundly perform subset analyses to compare concurrent and adjuvant versus adjuvant ADT was hindered. Despite these limitations, it is unlikely that a separate suitably powered phase III randomized controlled trial based on the central concept presented herein will ever be launched. Therefore, our findings potentially serve as the highest level of evidence that clearly support a preference for inclusion of adjuvant short-term ADT when administered with prostate-directed RT.

In conclusion, our findings have immediate and significant clinical implications on the management of localized PCa. They emphasize that a delay in initiating RT to allow receipt of neoadjuvant ADT is unnecessary and does not reduce long-term toxicity compared with an adjuvant approach in an unselected group of men treated with prostate-directed RT. Furthermore, adjuvant short-term ADT combined with prostate-directed RT was found to confer superior PFS reduced incidence of biochemical relapse and DM compared with neoadjuvant and concurrent ADT. Ongoing and future clinical research in localized PCa should consider these findings in trial design and conduct.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Prostate Radiotherapy With Adjuvant Androgen Deprivation Therapy (ADT) Improves Metastasis-Free Survival Compared to Neoadjuvant ADT: An Individual Patient Meta-Analysis

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APPENDIX

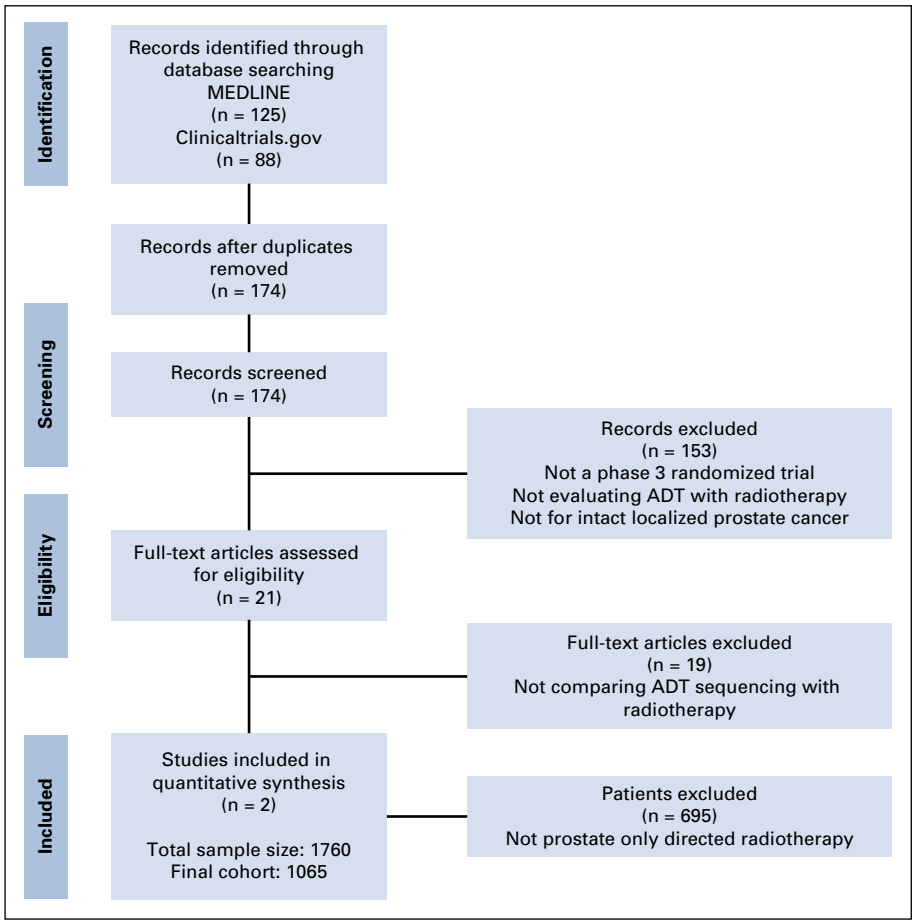

FIG A1. PRISMA diagram.

End Point	Variable	Group	Neoadjuvant Incidence/N	Adjuvant Incidence/N	15-yr Absolute Difference Neoadjuvant - Adjuvant (CI 95%)	HR (95%)	Interaction *P* value
OS							
	Age	< 65	38/102	50/120	0.02 (-0.13, 0.18)	0.90 (0.59, 1.37)	
		≥ 65	269/429	241/414	0.05 (-0.02, 0.13)	1.15 (0.96, 1.36)	.26
	T Stage	T1/T2a	94/225	95/223	0.02 (-0.10, 0.14)	1.00 (0.75, 1.33)	
		T2b/T2c	131/201	125/207	0.03 (-0.07, 0.14)	1.10 (0.86, 1.41)	.58
		T3/T4	82/105	71/104	0.14 (0.01, 0.27)	1.33 (0.97, 1.83)	.14
	PSA	< 10	86/176	83/191	0.10 (-0.03, 0.23)	1.18 (0.87, 1.60)	
		10-20	90/168	74/151	0.05 (-0.09, 0.18)	1.18 (0.86, 1.60)	.95
		20+	131/187	134/192	0.03 (-0.08, 0.13)	1.02 (0.80, 1.30)	.43
	Gleason	< 7	75/131	68/135	0.10 (-0.03, 0.24)	1.24 (0.89, 1.73)	
		7	165/315	153/304	0.04 (-0.05, 0.14)	1.07 (0.86, 1.33)	.47
		8-10	67/85	70/95	0.04 (-0.09, 0.16)	1.11 (0.79, 1.55)	.75
	Risk	High Risk	188/259	194/283	0.07 (-0.01, 0.16)	1.13 (0.92, 1.38)	
		Intermediate	119/271	97/251	0.04 (-0.07, 0.16)	1.15 (0.88, 1.51)	.90
MFS							
	Age	< 65	48/102	53/120	0.06 (-0.10, 0.21)	1.09 (0.74, 1.61)	
		≥ 65	276/429	245/414	0.07 (-0.01, 0.14)	1.18 (0.99, 1.40)	.71
	T Stage	T1/T2a	102/225	98/223	0.05 (-0.07, 0.17)	1.09 (0.82, 1.43)	
		T2b/T2c	135/201	127/207	0.05 (-0.06, 0.15)	1.14 (0.90, 1.46)	.75
		T3/T4	87/105	73/104	0.15 (0.02, 0.27)	1.36 (1.00, 1.86)	.21
	PSA	< 10	92/176	83/191	0.11 (-0.01, 0.24)	1.30 (0.97, 1.75)	
		10-20	93/168	77/151	0.04 (-0.09, 0.18)	1.14 (0.84, 1.55)	.50
		20+	139/187	138/192	0.06 (-0.04, 0.16)	1.10 (0.87, 1.40)	.38
	Gleason	< 7	77/131	71/135	0.09 (-0.05, 0.23)	1.20 (0.87, 1.66)	
		7	178/315	156/304	0.07 (-0.02, 0.16)	1.18 (0.96, 1.47)	.97
		8-10	69/85	71/95	0.06 (-0.05, 0.18)	1.13 (0.81, 1.57)	.96
	Risk	High Risk	199/259	200/283	0.09 (0.01, 0.17)	1.20 (0.98, 1.46)	
		Intermediate	125/271	98/251	0.06 (-0.05, 0.18)	1.22 (0.94, 1.59)	.92
PFS							
	Age	< 65	66/102	70/120	0.08 (-0.07, 0.23)	1.12 (0.80, 1.57)	
		≥ 65	250/429	222/414	0.07 (-0.02, 0.16)	1.29 (1.07, 1.55)	.58
	T Stage	T1/T2a	92/225	74/223	0.09 (-0.03, 0.21)	1.40 (1.03, 1.91)	
		T2b/T2c	129/201	131/207	0.03 (-0.08, 0.14)	1.09 (0.86, 1.40)	.27
		T3/T4	95/105	87/104	0.12 (0.02, 0.21)	1.51 (1.12, 2.02)	.56
	PSA	< 10	72/176	60/191	0.16 (0.01, 0.30)	1.52 (1.08, 2.15)	
		10-20	85/168	72/151	-0.00 (-0.15, 0.15)	1.14 (0.83, 1.56)	.29
		20+	159/187	160/192	0.06 (-0.01, 0.14)	1.25 (1.00, 1.56)	.51
	Gleason	< 7	79/131	67/135	0.13 (-0.02, 0.28)	1.38 (1.00, 1.91)	
		7	163/315	141/304	0.08 (-0.02, 0.19)	1.30 (1.04, 1.64)	.71
		8-10	74/85	84/95	0.03 (-0.06, 0.12)	1.16 (0.84, 1.58)	.55
	Risk	High Risk	222/259	235/283	0.08 (0.02, 0.15)	1.31 (1.08, 1.57)	
		Intermediate	94/271	57/251	0.12 (-0.00, 0.24)	1.65 (1.19, 2.30)	.25
DM							
	Age	< 65	19/102	18/120	0.03 (-0.09, 0.15)	1.25 (0.66, 2.37)	
		≥ 65	63/429	42/414	0.06 (0.01, 0.11)	1.48 (1.00, 2.18)	.89
	T Stage	T1/T2a	24/225	14/223	0.07 (0.00, 0.14)	1.80 (0.94, 3.45)	
		T2b/T2c	33/201	25/207	0.04 (-0.04, 0.12)	1.35 (0.80, 2.26)	.54
		T3/T4	25/105	21/104	0.02 (-0.09, 0.14)	1.15 (0.64, 2.04)	.10
	PSA	< 10	20/176	11/191	0.06 (-0.01, 0.13)	2.07 (1.00, 4.30)	
		10-20	18/168	16/151	0.00 (-0.08, 0.09)	0.99 (0.51, 1.94)	.81
		20+	44/187	33/192	0.08 (-0.01, 0.17)	1.40 (0.89, 2.19)	.46
	Gleason	< 7	11/131	13/135	-0.00 (-0.08, 0.08)	0.87 (0.39, 1.92)	
		7	52/315	25/304	0.10 (0.04, 0.16)	2.11 (1.31, 3.40)	.16
		8-10	19/85	22/95	-0.01 (-0.14, 0.13)	0.93 (0.50, 1.70)	.95
	Risk	High Risk	61/259	50/283	0.07 (-0.01, 0.14)	1.35 (0.93, 1.96)	
		Intermediate	21/271	10/251	0.04 (-0.01, 0.09)	1.96 (0.93, 4.14)	.84
PCSM							
	Age	< 65	18/102	25/120	0.01 (-0.12, 0.14)	0.87 (0.48, 1.58)	
		≥ 65	73/429	48/414	0.07 (0.02, 0.13)	1.52 (1.06, 2.18)	.94
	T Stage	T1/T2a	18/225	11/223	0.04 (-0.02, 0.11)	1.70 (0.81, 3.57)	
		T2b/T2c	39/201	37/207	0.03 (-0.05, 0.12)	1.07 (0.68, 1.66)	.33
		T3/T4	34/105	25/104	0.10 (-0.03, 0.23)	1.40 (0.84, 2.34)	.38
	PSA	< 10	18/176	10/191	0.08 (0.00, 0.16)	2.04 (0.95, 4.40)	
		10-20	18/168	16/151	0.01 (-0.08, 0.09)	1.01 (0.51, 1.96)	.53
		20+	55/187	47/192	0.08 (-0.02, 0.17)	1.25 (0.85, 1.84)	.50
	Gleason	< 7	16/131	16/135	0.03 (-0.06, 0.12)	1.04 (0.53, 2.07)	
		7	43/315	34/304	0.05 (-0.02, 0.12)	1.24 (0.79, 1.94)	.39
		8-10	32/85	23/95	0.14 (-0.01, 0.29)	1.64 (0.96, 2.79)	.11
	Risk	High Risk	76/259	63/283	0.10 (0.02, 0.18)	1.39 (1.00, 1.93)	
		Intermediate	15/271	10/251	0.02 (-0.04, 0.07)	1.36 (0.62, 3.02)	.32
BCF							
	Age	< 65	51/102	55/120	0.05 (-0.10, 0.20)	1.09 (0.75, 1.59)	
		≥ 65	163/429	113/414	0.12 (0.05, 0.19)	1.52 (1.20, 1.93)	.35
	T Stage	T1/T2a	68/225	44/223	0.11 (0.02, 0.20)	1.70 (1.16, 2.47)	
		T2b/T2c	83/201	75/207	0.06 (-0.04, 0.16)	1.14 (0.83, 1.55)	.53
		T3/T4	63/105	49/104	0.14 (-0.00, 0.28)	1.46 (1.01, 2.12)	.72
	PSA	< 10	40/176	31/191	0.07 (-0.02, 0.16)	1.48 (0.93, 2.35)	
		10-20	55/168	44/151	0.04 (-0.08, 0.15)	1.15 (0.78, 1.71)	.98
		20+	119/187	93/192	0.18 (0.07, 0.28)	1.51 (1.15, 1.98)	.04
	Gleason	< 7	53/131	36/135	0.16 (0.03, 0.28)	1.68 (1.10, 2.57)	
		7	111/315	81/304	0.10 (0.02, 0.18)	1.41 (1.06, 1.87)	.94
		8-10	50/85	51/95	0.06 (-0.09, 0.21)	1.22 (0.83, 1.80)	.78
	Risk	High Risk	153/259	131/283	0.15 (0.06, 0.23)	1.45 (1.15, 1.83)	
		Intermediate	61/271	37/251	0.08 (0.00, 0.16)	1.58 (1.05, 2.38)	.14

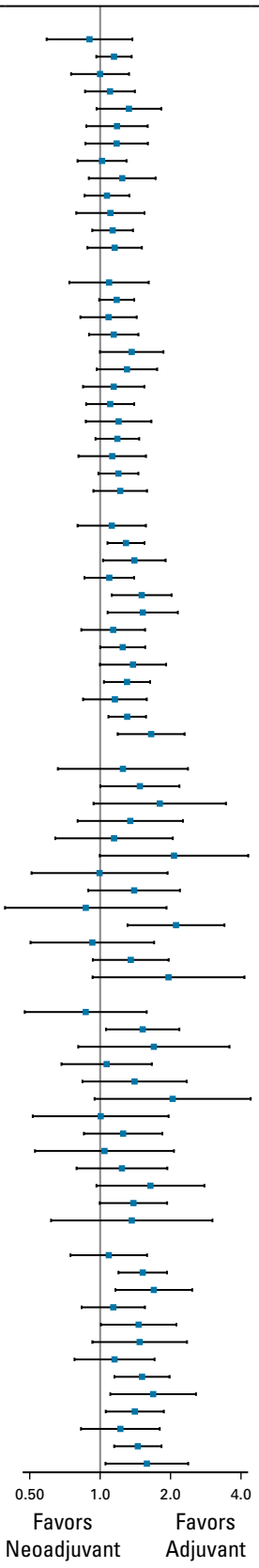

FIG A2. Subgroup analyses by end point.

End Point	Neoadjuvant Incidence/N	Adjuvant Incidence/N	15–yr Absolute Benefit of Adjuvant ADT (%, CI 95%)	15–yr RMST Benefit of Adjuvant ADT (Months, CI 95%)	HR (95%)	*P* value
Progression–free survival	316/531	292/534	7.0 (–0.4, 14.3)	12.5 (4.5, 20.5)	1.32 (1.12, 1.55)	.001
Biochemical failure	214/531	168/534	10.1 (3.8, 16.3)	12.2 (0.9, 23.4)	1.40 (1.14, 1.72)	.001
Distant metastasis	82/531	60/534	5.3 (0.5, 10.1)	2.6 (–4.6, 9.8)	1.40 (1.00, 1.96)	.051
Metastasis–free survival	324/531	298/534	6.7 (–3.2, 16.5)	3.9 (–3.0, 10.8)	1.17 (1.00, 1.38)	.045
Prostate cancer–specific mortality	91/531	73/534	5.8 (0.5, 11.0)	3.2 (–3.2, 9.6)	1.30 (0.96, 1.76)	.10
Overall survival	307/531	291/534	4.8 (–5.3, 14.8)	2.7 (–4.0, 9.3)	1.11 (0.95, 1.31)	.19

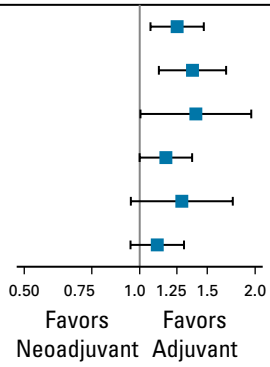

FIG A3. Oncologic outcomes after adjustment for clinical trial. ADT, androgen deprivation therapy; HR, hazard ratio.