VOLUME 36 · NUMBER 15 · MAY 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Intergroup Trial of Adjuvant Androgen Deprivation With or Without Mitoxantrone Plus Prednisone in Patients With High-Risk Prostate Cancer After Radical Prostatectomy: SWOG S9921

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Published at jco.org on April 6, 2018.

Clinical trial information: NCT00004124.

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0732-183X/18/3615w-1498w/$20.00

ABSTRACT

Purpose
Patients with high-risk prostate cancer after radical prostatectomy are at risk for death. Adjuvant androgen-deprivation therapy (ADT) may reduce this risk. We hypothesized that the addition of mitoxantrone and prednisone (MP) to adjuvant ADT could reduce mortality compared with adjuvant ADT alone.

Methods
Eligible patients had cT1-3N0 prostate cancer with one or more high-risk factors after radical prostatectomy (Gleason score [GS] ≥ 8; pT3b, pT4, or pN+ disease; GS 7 and positive margins; or preoperative prostate-specific antigen [PSA] > 15 ng/mL, biopsy GS score > 7, or PSA > 10 ng/mL plus biopsy GS > 6. Patients with PSA ≤ 0.2 ng/mL after radical prostatectomy were stratified by pT/N stage, GS, and adjuvant radiation plan and randomly assigned to ADT (bicalutamide and goserelin for 2 years) or ADT plus six cycles of MP. The primary end point was overall survival (OS). Median OS was projected to be 10 years in the ADT arm, requiring 680 patients per arm to detect a hazard ratio of 1.30 with 92% power and one-sided $\alpha = .05$.

Results
Nine hundred sixty-one eligible intent-to-treat patients were randomly assigned to ADT or ADT + MP from October 1999 to January 2007, when the Data Safety Monitoring Committee recommended stopping accrual as a result of higher leukemia incidence with ADT + MP. Median follow-up was 11.2 years. The 10-year OS estimates were 87% with ADT (expected 50%) and 86% with ADT + MP (hazard ratio, 1.06; 95% CI, 0.79 to 1.43). The 10-year estimate for disease-free survival was 72% for both arms. Prostate cancer was the cause of death in 18% of patients in the ADT arm and 22% in the ADT + MP arm. More patients in the MP arm died of other cancers (36% *v* 18% in ADT alone arm).

Conclusion
MP did not improve OS and increased deaths from other malignancies. The DFS and 10-year OS in these patients treated with 2 years of ADT were encouraging compared with historical estimates, although a definitive conclusion regarding value of ADT may not be made without a nontreatment control arm.

J Clin Oncol 36:1498-1504. © 2018 by American Society of Clinical Oncology

ASSOCIATED CONTENT

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DOI: https://doi.org/10.1200/JCO.2017.76.4126

Data Supplement
DOI: https://doi.org/10.1200/JCO.2017.76.4126

DOI: https://doi.org/10.1200/JCO.2017.76.4126

INTRODUCTION

Despite significant progress, prostate cancer continues to be a major cause of morbidity and mortality in the United States, resulting in 29,430 deaths in 2018, which represents the second leading cause of cancer death in American men.[1] Metastatic disease continues to be universally lethal; hence, enhancing multimodal therapy for high-risk, locally advanced prostate cancer will likely have a better effect on prolonging survival and reducing prostate cancer–related deaths and suffering.

In patients with clinically organ-confined prostate cancer, freedom from prostate-specific antigen (PSA) relapse at 5 years is associated with Gleason score, PSA level, pathologic tumor (T) and node (N) stage, and status of the surgical margin. Preoperative PSA ≥ 20 ng/mL, Gleason score (GS) ≥ 8, seminal vesicle or extensive

Table 1. Baseline Patient Characteristics for All Eligible Patients on S9921

Characteristic	ADT Only (n = 481)	ADT + MP (n = 480)	All Patients
Median age, years (range)	60 (40-82)	60 (40-86)	60 (40-86)
Median PSA at prostatectomy, ng/mL (first and third quartiles)	7.9 (5.1, 12.3)	7.4 (5.1, 12.7)	7.7 (5.1, 12.5)
Race			
White	399 (83)	411 (86)	810 (84)
Black	66 (14)	50 (10)	116 (12)
Asian	6 (1.3)	11 (2.3)	17 (1.8)
Other	10 (2.1)	8 (1.7)	18 (1.9)
Hispanic	25 (5)	30 (6)	55 (6)
Extent of disease			
N1	79 (16)	83 (17)	162 (17)
≥ T3 but N0	293 (61)	306 (64)	599 (62)
Organ confined	109 (23)	91 (19)	200 (21)
Positive margins	316 (66)	293 (61)	609 (63)
Intent to receive adjuvant RT	130 (27)	127 (26)	257 (27)
Gleason score			
≤ 6	10 (2)	12 (3)	22 (2)
7	215 (45)	220 (46)	435 (45)
8-10	256 (53)	248 (52)	504 (52)
Risk groups			
Grp 1: Gleason ≤ 7 with positive margins or PSA > 10 ng/mL	126 (26)	101 (21)	227 (24)
Grp 2: Gleason	276 (57)	296 (62)	572 (60)
Grp 3: Node positive	79 (16)	83 (17)	162 (17)

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: ADT, androgen-deprivation therapy; MP, mitoxantrone and prednisone; PSA, prostate-specific antigen; RT, radiation therapy.

surgical margin involvement, extraprostatic extension (pT3a), and/or nodal metastases define a high-risk group of patients with a 5-year PSA relapse rate of > 50%.[2-6] Short-term neoadjuvant androgen-deprivation therapy (ADT) before radical prostatectomy reduced positive margins but had no effect on disease-free survival (DFS) or overall survival (OS) in several underpowered trials.[7] In the setting of high-risk localized or locally advanced disease, longer term adjuvant ADT improved OS in combination with radiation therapy.[8]

At the time of study design, a multitargeted strategy using chemohormonal therapy was deemed an important step in managing this disease on the basis of emerging data regarding mechanism of progression on ADT and the proven successes of modestly active chemotherapy in other solid tumors, such as breast and colon, when advanced to earlier stages. In the 1990s, estramustine and mitoxantrone were the key available agents. Despite the apparent improved response rates with estramustine, no large-scale or phase III data were available, whereas mitoxantrone was approved by the US Food and Drug Administration (FDA) for metastatic castration-resistant prostate cancer on the basis of phase III trial data demonstrating a higher proportion and duration of palliative, objective, and PSA response rates in favor of mitoxantrone plus prednisone compared with prednisone alone.[9] On the basis of the totality of data in 1999, we hypothesized that adjuvant mitoxantrone plus prednisone (MP) combined with 2 years of ADT could further reduce mortality and improve OS in high-risk patients with prostate cancer after radical prostatectomy. At the time of study design, the OS benefit of adjuvant radiation therapy was uncertain because the Southwest Oncology Group (SWOG) randomized trial (S8794) was still ongoing. Given the available data, the use of adjuvant radiation therapy was allowed on study, specifically for margin-positive patients. This was included as stratification by intention to treat.

METHODS

Eligibility Criteria

Eligible men had to have cT1-3N0M0 (negative imaging; bone scan required for PSA ≥ 20 ng/mL) and operable-for-cure prostate cancer, radical prostatectomy within 120 days before registration, and one or more of the following criteria: a pathologic Gleason score (GS) ≥ 8; pT3b, pT4, or N1 disease; pathologic GS of 7 and positive margins; or any of the following preoperative findings (in patients who received neoadjuvant ADT): a preoperative PSA of > 15 ng/mL, biopsy GS > 7, or PSA of > 10 ng/mL plus a biopsy GS > 6. All patients had to have postoperative PSA ≤ 0.2 ng/mL before any hormonal therapy.

Random Assignment

Patients were randomly assigned 1:1 to ADT (arm 1) or ADT + MP (arm 2) at the SWOG Statistical Center. The random assignment was dynamically balanced[10] for the following three stratification factors: pathologic stage of disease (organ confined [pT2a-b with either positive or negative surgical margins] but N0 *v* not organ confined [≥ pT3] but N0 *v* N1 [any T]); GS (< 7 *v* 7 *v* > 7); and adjuvant radiation planned (yes *v* no).

Treatment Plan

Patients randomly assigned to arm 1 received ADT with goserelin (10.8 mg subcutaneously every 3 months) plus bicalutamide 50 mg orally daily for 24 months. Patients assigned to arm 2 received ADT plus mitoxantrone 12 mg/m^2 intravenously every 3 weeks for a total of six cycles and prednisone 5 mg orally twice daily.

Statistical Analysis

The primary end point was OS, defined as time from random assignment to death as a result of any cause. A secondary end point was DFS, defined as time from random assignment to recurrence or death as a result of any cause. Recurrence was defined as a serum PSA level > 0.2 ng/mL measured on three consecutive occasions, a positive bone scan, or other radiographic evidence of progression. Assuming 9.5 years of accrual, an

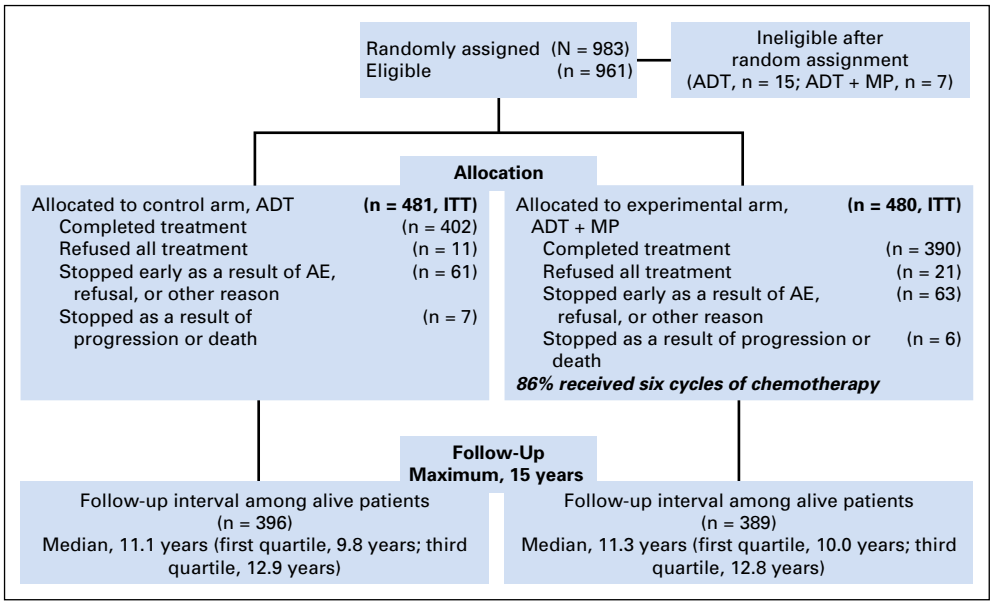

Fig 1. CONSORT diagram. ADT, androgen-deprivation therapy; AE, adverse event; ITT, intent-to-treat; MP, mitoxantrone and prednisone.

additional 4 years of follow-up, and 1,360 eligible patients, the study was designed to have 92% power to detect a 30% increase in median OS from 10 years to 13 years with a one-sided $\alpha = .05$. The study was monitored by the SWOG Data Safety Monitoring Committee (DSMC). The following three formal interim analyses were planned: after 700 patients were randomly assigned; when 50% of the total expected deaths had occurred; and 2.5 years after accrual was completed. For both OS and DFS end points, stratification factors were handled as covariates in a Cox model with the addition of an indicator for protocol treatment.

Time to testosterone recovery was assessed in men who received the full 2 years of ADT and had complete reporting of testosterone values, which were measured every 6 months until the level was greater than the institutional lower limit of normal.

RESULTS

Between October 15, 1999, and January 12, 2007, 983 patients were enrolled and randomly assigned; 961 patients were eligible and form the basis of our intent-to-treat primary analysis. The protocol was approved by each institution's review board, and all patients signed an informed consent form. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975.

As a result of patient safety issues related to an increased incidence of acute myelogenous leukemia, on January 12, 2007, the SWOG DSMC recommended that enrollment onto this trial stop permanently and that patients randomly assigned to the chemotherapy arm should stop receiving mitoxantrone if still on protocol therapy.[11] Patients on both arms were encouraged to complete the 2 years of ADT. Because accrual would not be completed and chemotherapy was stopped, the DSMC released the trial to the study investigators to report the results of the trial as they saw fit.

Four hundred eighty-one patients were randomly assigned to arm 1, and 480 patients were assigned to arm 2. Both arms were balanced with regard to relevant risk criteria (Table 1). The median age was 60 years, median presurgical PSA was 7.7 ng/mL, 16% of patients were nonwhite, 17% had pN1, 52% had GS $\geq$ 8, 62% had

Table 2. Adverse Events in Eligible Patients Who Received Any Protocol Treatment Including Any Toxicity With at Least One Grade 3 Event Reported

	No. of Patients					
	ADT (n = 469)			ADT + MP (n = 460)		
Adverse Event	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Anxiety	3	0	0	0	1	0
Depression	8	3	0	6	1	0
Fatigue	6	0	0	11	1	0
Hyperglycemia	3	2	0	10	3	0
Hypoxia	0	0	0	3	1	0
Leukopenia	1	0	0	110	39	0
Pain	2	0	0	1	1	0
Second primary tumor	0	0	0	0	6	0
DVT/embolism	2	0	0	2	1	0
Maximum any adverse event	136	5	0	210	47	1

Abbreviations: ADT, androgen-deprivation therapy; DVT, deep vein thrombosis; MP, mitoxantrone and prednisone.

pT3a/bN0, 24% had GS ≤ 7 with positive margins or PSA > 10 ng/mL, and 63% had positive margins. Four hundred two of 481 patients on arm 1 and 390 of 480 patients on arm 2 completed protocol therapy, with 86% of the patients on arm 2 receiving six cycles of MP (Fig 1).

The intent to treat with adjuvant radiation therapy was declared at the time of random assignment in 257 patients (27%), but less than half of these patients (n = 95) actually reported receiving treatment. In addition, follow-up radiation (for treatment failure) was not reported. Therefore, the exact contribution of radiation therapy remains uncertain.

Adverse Events

Table 2 lists the most frequent grade ≥ 3 adverse events. Leukopenia was the only adverse event that occurred in ≥ 5% of patients in arm 2. Of note, there was a lack of significant cardiovascular events in both arms (Appendix Tables A1 and A2, online only).

Testosterone Recovery

The median time to testosterone recovery (≥ 50 ng/mL) measured from completion of ADT was 9.5 months (95% CI, 9 to 11 months). The 6-, 12-, and 18-month overall testosterone recovery rates to greater than the castrate range (> 50 ng/mL) were 28% (95% CI, 6% to 71%), 75% (95% CI, 51% to 90%), and 90% (95% CI, 70% to 97%), respectively.

OS and DFS

With a median follow-up time of 11.2 years, the 10-year OS estimates were 87% for ADT and 86% for ADT + MP (Fig 2A). There was no statistically significant difference in OS distributions (hazard ratio [HR; MP + AD *v* AD], 1.06; 95% CI, 0.79 to 1.43; $P = .70$). In terms of survival, interactions of stratification factors with treatment were not significant (extent of disease, $P = .57$; GS, $P = .19$; intent to receive adjuvant radiation, $P = .99$). Ten-year DFS rate was

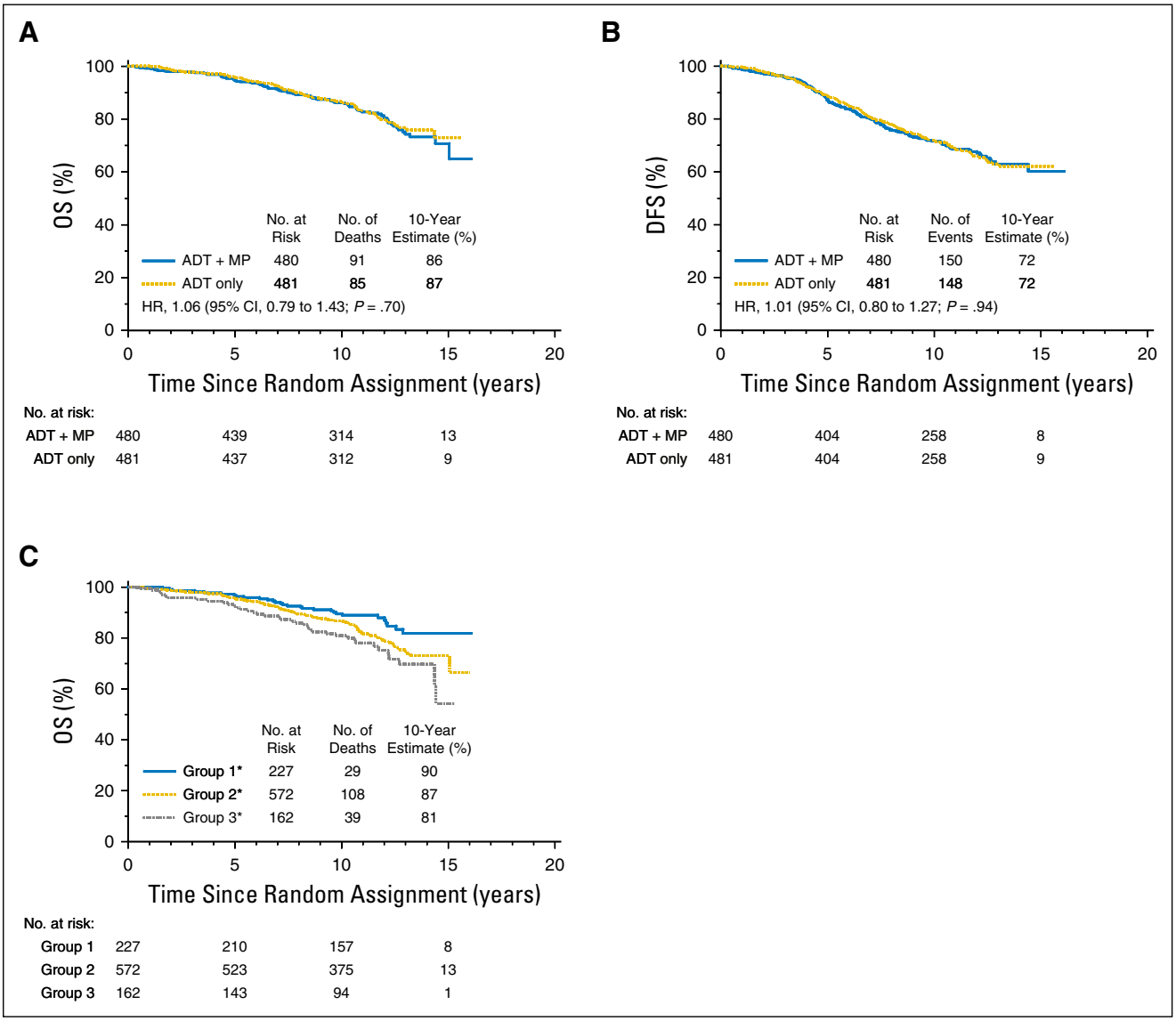

Fig 2. (A) Intent-to-treat (ITT) overall survival (OS) by treatment arm. (B) ITT disease-free survival (DFS) by treatment arm. (C) OS by risk group, pooled arms. (*) Risk groups defined in Table 1. ADT, androgen-deprivation therapy; HR, hazard ratio; MP, mitoxantrone and prednisone.

Table 3. Cause of Death by Treatment Arm

Cause of Death	ADT	ADT + MP
Total No. of deaths	85	91
Cause of death, %		
Prostate cancer	18	22
Unknown but not prostate cancer	22	14
Unknown	14	12
Other causes	28	16
Other cancers	18	36
Other cancers that resulted in death, No.		
Lung	3	7
Leukemia	1	5
Pancreas	0	5
GI	5	7
Kidney	2	3
Brain	1	1
Other	3	4

Abbreviations: ADT, androgen-deprivation therapy; MP, mitoxantrone and prednisone.

72% in both arms (HR, 1.01; 95% CI, 0.80 to 1.27; $P = .94$; Fig 2B). In the ADT + MP arm, 62% of the DFS events were recurrences and 38% were death without recurrence. In the ADT arm, 57% of the DFS events were recurrences and 43% were death without recurrence. Therefore, in both arms, approximately 40% of DFS events were from deaths unrelated to prostate cancer.

Table 3 lists the causes of death in both arms. Of note, prostate cancer was the cause of death in 18% of patients in the ADT arm and 22% of patients in the ADT + MP arm. More patients in ADT + MP arm died of other cancers, such as leukemia, lung, and pancreas cancer, compared with the ADT alone arm (36% *v* 18%, respectively). Table 4 lists the OS and DFS outcomes by risk group and treatment arm. The three risk group interaction with treatment arm was nonsignificant ($P = .23$), suggesting there is no compelling evidence of a treatment effect in any of these subsets of patients. Figure 2C shows the Kaplan-Meier survival curves by risk group, pooling treatment arms. Patients with positive lymph nodes had an 81% 10-year survival rate in both arms. Patients with a GS of ≥ 8 or stage T3b disease had a 10-year survival rate of 88% in the ADT arm and 85% in the ADT + MP arm. The remaining risk group had 10-year survival rate of 87% in the ADT arm and 93% in the ADT + MP arm.

DISCUSSION

The SWOG S9921 trial was designed in the late 1990s using risk criteria of the time, specifically preoperative PSA level, pT and N stage, and tumor GS. The majority of patients in both arms had N1, pT3b, or GS ≥ 8 disease, which are high-risk factors by today's standards. The DFS and OS rates were higher than anticipated in both arms regardless of risk group. This could be a function of risk definition, and although there was no control arm of no therapy, the effect of 2 years of ADT cannot be ruled out.

The role of adjuvant ADT was emerging at the time of S9921 study design. Messing et al[12] had reported the effects of immediate versus delayed permanent (orchiectomy or continuous goserelin) ADT in 98 men who had undergone radical prostatectomy with lymph node dissection and proven nodal metastases. At the 7-year follow-up, seven of 47 men who received immediate ADT had died (three from prostate cancer) compared with 18 of 51 men who received ADT upon disease progression (16 from prostate cancer). An update published with 11.9 years of follow-up continued to show significant OS benefit for immediate ADT compared with delayed ADT (HR, 1.85; $P = .04$) and an even more impressive benefit for prostate cancer–specific survival (HR, 4.09, $P < .001$).[13] Similarly, Pilepich et al[14] reported on the use of adjuvant goserelin indefinitely after curative intent radiotherapy in clinical stage T3 patients or those with documented nodal involvement. The 5-year DFS among men receiving adjuvant ADT after radiation therapy was 53% compared with 20% on the observation arm using a PSA cutoff value of 1.5 ng/mL as an indication of progression at ≥ 1 year. When formally reported with longer term follow-up, this study (Radiation Therapy Oncology Group 85-31) revealed a disease-specific mortality at 10 years of 16% in the ADT arm compared with 22% in the observation arm ($P = .0052$).[14]

MP was chosen for this study because it had demonstrated clinical benefit in metastatic castration-resistant prostate cancer, leading to FDA approval. Of note, a small randomized trial from the early 1990s that included patients with T3-4 prostate cancer compared ADT with or without mitoxantrone.[15] In this small study, in patients with localized prostate cancer, the combination of mitoxantrone and ADT was found to be superior to ADT alone (median OS, 80 *v* 36 months, respectively; $P = .04$). However, in

Table 4. Overall and Disease-Free Survival by Risk Group

Risk Group	10-Year Overall Survival (All-Cause) Estimate				10-Year Disease-Free Survival Estimate			
	ADT + MP (%)	ADT (%)	HR (95% CI; ADT + MP v ADT)	*P*	ADT + MP (%)	ADT (%)	HR (95% CI)	*P*
Group 1 (29 deaths, 46 DFS events, 227 patients at risk)	93	87	0.63 (0.29 to 1.35)	.23	88	77	0.55 (0.30 to 1.02)	.06
Group 2 (108 deaths,186 DFS events, 572 patients at risk)	85	88	1.24 (0.85 to 1.82)	.27	68	74	1.16 (0.87 to 1.54)	.33
Group 3 (39 deaths, 64 DFS events, 162 patients at risk)	81	81	0.89 (0.48 to 1.68)	.73	66	55	0.79 (0.48 to 1.29)	.34
High-grade disease Gleason score 8-10 (93 deaths, 154 DFS events, 424 patients at risk)	84	86	1.24 (0.82 to 1.87)	.30	65	70	1.15 (0.84 to 1.58)	.37

NOTE. Risk group interaction with treatment: overall survival, $P = .23$ (2 *df* test); disease-free survival, $P = .07$ (2 *df* test). Group 1: Gleason score ≤ 7 with positive margins or preoperative prostate-specific antigen > 10 ng/mL; group 2: Gleason score ≥ 8 or pathologic stage T3b; group 3: positive nodes.
Abbreviations: ADT, androgen-deprivation therapy; DFS, disease-free survival; HR, hazard ratio; MP, mitoxantrone and prednisone.

our study, MP did not improve DFS or OS and was associated with a higher leukemia rate, which led to early termination of the study by the SWOG DSMC.[11] Surprisingly, it was also associated with double the rate of deaths from other malignancies compared with the ADT only arm (36% *v* 18%, respectively). Although this was not a planned analysis and this finding may be a result of chance, it is important to note this finding for further study and validation.

Although the prostate cancer risk criteria used in this trial continue to be used today, it is notable that the majority of deaths in this trial were not related to prostate cancer. A combination of earlier detection and changes in tumor grade assignment (grade inflation) may have played a role.[16] With further experience, it is possible that incorporation of molecular markers of disease prognosis may enhance the ability to better identify patients whose prostate cancer progression risk is sufficiently high so as to be more likely to benefit from adjuvant therapy.[17]

In 2004, docetaxel was approved by the FDA on the basis of OS improvement.[18,19] Since then, five additional agents (cabazitaxel, sipuleucel-T, abiraterone acetate + prednisone, enzalutamide, and radium-223) have been approved to treat metastatic castration-resistant prostate cancer. Two of these agents, docetaxel and abiraterone acetate + prednisone, have also demonstrated an unprecedented OS advantage in randomized phase III trials in metastatic hormone-sensitive prostate cancer.[20,21] These data highlight the fact that the effect of advanced androgen receptor–targeted and multitargeted therapies on survival will likely be greater when incorporated into earlier stages of disease. As such, this provides an imperative to evaluate these and other active agents in carefully preselected, newly diagnosed, high-risk patients. However, given the high DFS and OS seen in the current study, better risk stratification including molecular prognostication is clearly necessary to power such studies.

Interestingly, this trial demonstrated that even patients with pN1 disease (similar to the trial by Messing et al[13]) or other high-risk criteria have a good prognosis with 2 years of ADT. Thus, balancing risks versus benefits from systemic therapy is clinically critical.

This intergroup, randomized, phase III clinical trial demonstrated the feasibility of delivering adjuvant therapy in high-risk patients with prostate cancer after radical prostatectomy. However, it was closed to enrollment by the DSMC before it was fully accrued as a result of more acute leukemia cases noted in the ADT + MP arm. Leukemia was not previously associated with mitoxantrone use in prostate cancer, but this association is known and the previous use of mitoxantrone in prostate cancer was largely limited to late-stage metastatic castration-resistant prostate cancer, which has a poor prognosis. Surprisingly, we observed an increased incidence of other cancers in the ADT + MP arm, including lung and GI cancers. Mitoxantrone is also occasionally used in nononcology settings, including in the treatment of multiple sclerosis. A recent observational cohort study of 676 patients with multiple sclerosis treated with mitoxantrone noted an increased incidence of leukemia and colorectal cancer on the basis of population estimates. The study also reported two pancreatic cancers and two lung cancers.[22]

The findings from this trial clearly highlight several important lessons that should be taken into consideration in future clinical trials. First, despite high-risk disease features, patients with prostate cancer do live many years, and most do not die of prostate cancer. Second, benefits of systemic therapy cannot be extrapolated from different disease stages; safety in end-stage disease cannot be assumed in earlier stages, as reflected by the increased risk of leukemia and other malignancies in the mitoxantrone arm in this trial, a risk that was not previously noted in patients with metastatic castration-resistant prostate cancer. Finally, it is absolutely critical to have adequate follow-up in adjuvant therapy prostate cancer trials to better inform regarding the true value and risks of an experimental intervention.

In conclusion, in high-risk patients with prostate cancer, ADT + MP did not improve survival compared with ADT. In both arms, the 10-year OS rate was approximately 87%, compared with our pretrial estimate of 50%. Whether ADT is helpful in our study population compared with no treatment cannot be definitively answered because there was no control arm without ADT, but the OS and DFS rates observed here were clearly greater than those projected using the entry criteria and knowledge during the study's design. This trial provides important information that adds to other recent clinical investigations in the use of intensified and earlier treatment in high-risk patients with prostate cancer to inform patient and physician decision making.

In a rapidly changing genomics and therapeutic landscape, the way forward in the adjuvant setting will include incorporating genomic predictors of poor outcome, use of surrogate intermediate end points of clinical benefit, and incorporation of novel therapies including new androgen receptor–targeted agents with demonstrated effect on OS in metastatic prostate cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Support

Supported by the National Cancer Institute of the National Institutes of Health under Grants No. CA180888, CA180819, CA180820, CA180821, CA180801, CA180834, CA180830, CA189953, CA180835, CA128567, CA190002, CA180846, CA189860, CA189804, CA189856, CA189858, CA189808, CA180828, CA189872, CA189822, CA189853, CA189848, CA189971, CA189952, CA46282, CA46368, CA35192, CA11083, CA35119, CA45450, CA74647, CA35128, CA35262, CA68183, CA37981, CA22423, CA58686, CA04919, CA46136, CA76132, CA76447, CA46113, CA12644, CA16385, and CA58723. Also supported in part by AstraZeneca Pharmaceuticals and Immunex Corporation (Amgen).

Prior Presentation

Presented at the 2017 ASCO Genitourinary Cancers Symposium, Orlando, FL, February 16-18, 2017; and the 53rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 2-6, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase III Intergroup Trial of Adjuvant Androgen Deprivation With or Without Mitoxantrone Plus Prednisone in Patients With High-Risk Prostate Cancer After Radical Prostatectomy: SWOG S9921

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Patents, Royalties, Other Intellectual Property: Systems and Methods for Tissue Imaging, 3676 Our File: Serial Number: UM-14437/US-1/PRO 60/923,385 UM-14437/US-2/ORD 12/101,753US 8,185,186 (US patent No.); Systems and Methods for Tissue Imaging (issued patent); EP 08745653.9 (EP application number) Systems and Methods for Tissue Imaging (pending); CA 2683805 (Canadian application number) Systems and Methods for Tissue Imaging (pending); US 13/362,500 (US application number) Systems and Methods for Tissue Imaging (continuation application of US 8,185,186); Method of Treating Cancer, Docket No: Serial Number: 224990/10-016P2/311733 61/481/671, Application Filed on: 5/2/2011, Dual Inhibition of MET and VEGF for the Treatment of Castration-Resistant Prostate Cancer and Osteoblastic Bone Metastases, Applicant/Proprietor Exelixis, Application No/Patent No. 11764665.4- 1464, Application No./Patent No. 11764656.2-1464 Application Filed on: 26/9/2011
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Patents, Royalties, Other Intellectual Property: The University of Colorado has filed two patents in which I am an inventor. These are related to early-stage bladder cancer treatment and detection. Neither is commercialized or licensed at this time.
Travel, Accommodations, Expenses: Bavarian Nordic, GTx

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Appendix

Table A1. Patients With a Given Type and Grade of Cardiovascular Adverse Event Regardless of Attribution to Any Drug

	No. of Patients									
	Bicalutamide + Goserelin (n = 469)					Mitoxantrone + Prednisone + Bicalutamide + Goserelin (n = 460)				
Adverse Event	Unknown	≤ Grade 2	Grade 3	Grade 4	Grade 5	Unknown	≤ Grade 2	Grade 3	Grade 4	Grade 5
Cardiovascular (arrhythmia)										
Arrhythmia, NOS	0	469	0	0	0	0	460	0	0	0
Conduction abnormality/block	0	468	1	0	0	0	459	1	0	0
Palpitations	0	469	0	0	0	0	460	0	0	0
Sinus bradycardia	0	469	0	0	0	0	459	1	0	0
Supraventricular arrhythmia	0	469	0	0	0	0	458	1	1	0
Ventricular arrhythmia	0	468	1	0	0	0	460	0	0	0
Cardiovascular (general)										
Cardiac ischemia/infarction	0	467	2	0	0	0	458	1	1	0
Cardiovascular, other	0	468	1	0	0	0	459	1	0	0
Edema	0	469	0	0	0	0	460	0	0	0
Hypertension	0	455	14	0	0	0	449	11	0	0
Hypotension	0	469	0	0	0	0	460	0	0	0
LVEF decrease/CHF	0	468	1	0	0	0	457	3	0	0
Myocarditis	0	469	0	0	0	0	459	1	0	0
Pericardial effusion/pericarditis	0	469	0	0	0	0	460	0	0	0
Phlebitis	0	469	0	0	0	0	460	0	0	0
Thrombosis/embolism	0	467	2	0	0	0	457	2	1	0
Cardiac troponin T increase	0	469	0	0	0	0	460	0	0	0

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NOS, not otherwise specified.

Table A2. Patients With a Given Type and Grade of Cardiovascular Adverse Event With Events Unlikely or Not Related to Treatment Excluded

	No. of Patients									
	Bicalutamide + Goserelin (n = 469)					Mitoxantrone + Prednisone + Bicalutamide + Goserelin (n = 460)				
Adverse Event	Unknown	≤ Grade 2	Grade 3	Grade 4	Grade 5	Unknown	≤ Grade 2	Grade 3	Grade 4	Grade 5
Cardiovascular (arrhythmia)										
Arrhythmia, NOS	0	469	0	0	0	0	460	0	0	0
Conduction abnormality/block	0	468	1	0	0	0	460	0	0	0
Palpitations	0	469	0	0	0	0	460	0	0	0
Sinus bradycardia	0	469	0	0	0	0	459	1	0	0
Supraventricular arrhythmia	0	469	0	0	0	0	459	1	0	0
Ventricular arrhythmia	0	468	1	0	0	0	460	0	0	0
Cardiovascular (general)										
Cardiac ischemia/infarction	0	468	1	0	0	0	460	0	0	0
Cardiovascular, other	0	469	0	0	0	0	459	1	0	0
Edema	0	469	0	0	0	0	460	0	0	0
Hypertension	0	461	8	0	0	0	455	5	0	0
Hypotension	0	469	0	0	0	0	460	0	0	0
LVEF decrease/CHF	0	469	0	0	0	0	457	3	0	0
Myocarditis	0	469	0	0	0	0	459	1	0	0
Pericardial effusion/pericarditis	0	469	0	0	0	0	460	0	0	0
Phlebitis	0	469	0	0	0	0	460	0	0	0
Thrombosis/embolism	0	467	2	0	0	0	457	2	1	0
Cardiac troponin T increase	0	469	0	0	0	0	460	0	0	0

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; NOS, not otherwise specified.