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ORIGINAL ARTICLE

A phase 2 multimodality trial of docetaxel/prednisone with sunitinib followed by salvage radiation therapy in men with PSA recurrent prostate cancer after radical prostatectomy

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BACKGROUND: In men with high Gleason PC and rapid PSA progression after surgery, failure rates remain unacceptably high despite salvage radiation. We explored a novel multimodality approach of docetaxel with anti-angiogenic therapy before salvage radiotherapy (RT).

METHODS: This was a phase 2 single-arm prospective open-label trial with historic controls. Eligible men had a rising PSA of 0.1–3.0 ng ml^{-1} within 4 years of radical prostatectomy, no metastases except resected nodal disease, no prior androgen-deprivation therapy (ADT) and Gleason 7–10. Men received four cycles of docetaxel 70 mg m^{-2} every 3 weeks with low dose prednisone and sunitinib 37.5 mg daily for 14/21 days each cycle, with no ADT. Salvage prostate bed RT (66 Gy) started at day 100. The primary end point was progression-free survival (PFS) rate at 24 months. Safety data, quality of life (QOL) and dose-limiting toxicities (DLTs) were measured over time.

RESULTS: Thirty-four men accrued in this multi-institutional clinical trial: 24% of men were node positive, 47% were Gleason 8–10, median PSA at entry was 0.54. The trial was terminated prematurely owing to excess DLTs (nine) including grade 3 hand–foot syndrome ($n=4$), neutropenic fever ($n=2$), AST increase ($n=1$), fatigue ($n=1$) and vomiting with diarrhea ($n=1$). PFS rate at 24 months was 51% (95% CI: 33, 67%) with a median PFS of 26.2 months (95% CI: 12.5, —). Six men (17.6%) had an undetectable PSA at 2 years.

CONCLUSIONS: Sunitinib and docetaxel/prednisone followed by salvage RT resulted in excess pre-specified DLTs. Although nearly half of the men experienced durable disease control, efficacy was not greater than expected with radiation alone. The use of the intermediate end point of PFS in this salvage setting permitted an early decision on further development of this combination.

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INTRODUCTION

Although systemic treatment options have improved for men with castration-resistant PC (CRPC), the treatment of men with biochemical (PSA) recurrence following radical prostatectomy (RP) remains unsatisfying, given the high rates of recurrent disease despite salvage radiotherapy (RT).[1] In most large series, the rate of distant or PSA recurrence is ~60–70% following salvage RT,[1,2] particularly in those men with higher PSA levels, rapid PSA kinetics, higher grade or stage disease and negative surgical margins.[1,3] Given the significant risk of nonlocal progression in this population, effective systemic therapies are needed.

In breast cancer, multimodality therapy represents the standard-of-care approach, including surgery followed by adjuvant systemic chemotherapy and RT for optimal local control, and targeted hormonal or biologic therapy for a defined interval of time to reduce the ongoing risk of systemic disease recurrence. In men with high-risk PC, however, adjuvant and salvage therapy using multiple modalities, including surgery, radiation and systemic non-hormonally based therapy remains experimental. Although uncontrolled trials suggest a modest benefit of androgen-deprivation therapy (ADT) in the salvage setting,[3] randomized trials of hormonal therapy in this setting have not been published (that is, RTOG 9601) or are currently ongoing (that is, RTOG 0534, RADICALS) and thus the role of ADT is presently unclear. Although RT alone in the salvage setting may reduce the risk of PSA and local recurrence, it has an unclear benefit on the reduction of metastatic disease and overall survival.[4,5] Retrospective series suggest that a survival benefit with radiation may be seen in men with positive surgical margins, but benefits have been seen across nearly all subgroups.[3,6–8]

Sunitinib is an orally bioavailable inhibitor of the tyrosine kinase domains of vascular endothelial growth factor receptor, platelet derived growth factor and c-kit.[9] The combination of sunitinib and docetaxel demonstrated additive efficacy in preclinical and clinical studies of CRPC.[10–12] Although sunitinib did not improve survival as a single agent in a phase 3 trial of men with chemorefractory

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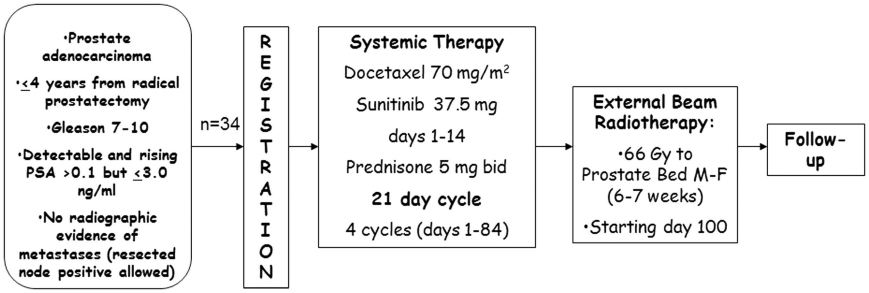

Figure 1. Schema for the multimodality trial ($n = 34$ final sample size).

CRPC, this does not exclude a role for combination therapy in earlier settings.[13]

We thus designed a phase 2 trial of multimodality therapy using docetaxel-based chemotherapy with concurrent sunitinib followed by RT for men with PSA relapse after RP and who have a high risk of further PSA failure. It is possible that the early use of docetaxel-based chemotherapy may improve systemic and PSA relapse rates in this micrometastatic population and subsequent RT may provide improved local control, given the survival benefit seen with docetaxel in men with mCRPC and in the metastatic castration-sensitive setting.[14,15]

MATERIALS AND METHODS

Patient eligibility

This was a multi-institutional, non-blinded, single-arm phase II trial (NCT00734851) conducted through the Department of Defense Prostate Cancer Clinical Trials Consortium (DOD PCCTC) across three trial sites. Eligibility included men with prostate adenocarcinoma and evidence of recurrent disease as measured by rising PSA (defined by one or more PSA values greater than the nadir value after RP, separated by >4 weeks), and no radiographic evidence of metastatic disease, although patients with node-positive resected disease at the time of RP were eligible. Inclusion criteria also included a rising PSA $\leqslant 3.0\,\mathrm{ng\,ml^{-1}}$ and $\geqslant 0.1\,\mathrm{ng\,ml^{-1}}$ within 2 weeks of registration; Gleason sum at radical prostatectomy of 7–10; $\geqslant 18$ years of age; adequate renal, hepatic and hematologic laboratory parameters; KPS $\geqslant 80$; and peripheral neuropathy $\leqslant$ grade 1. All the patients provided informed consent under an institutional review board approval.

Exclusion criteria included radiographic evidence of metastatic disease; cardiovascular comorbidities (major cardiovascular event within 12 months of recent hemorrhage or non-healing wound, class 2–4 American Heart Association heart disease) that would preclude the use of systemic chemotherapy; prior systemic therapy or radiation therapy; non-adenocarcinoma histology; uncontrolled hypertension ($>140/90$ mm Hg); anticoagulation with warfarin; and inability to absorb oral medications.

Objectives

The primary objective of this trial was the rate of progression-free survival (PFS) at 24 months, defined as the proportion of subjects without any of either (1) PSA rise $\geqslant 0.2\,\mathrm{ng\,ml^{-1}}$ above the post-RT nadir, confirmed 4 weeks later; (2) continued consecutive confirmed rise in PSA following study treatment if no nadir was experience; (3) evidence of clinical progression or initiation of systemic therapy; or (4) death. Secondary objectives of this study included the following: (1) PSA PFS over time and at 24 and 36 months; including only PSA-based end points or death, whichever occurred first; (2) local recurrence rates, defined as men with locally recurrent disease confirmed pathologically within the radiation field, estimated at 24 and 36 months; (3) metastasis-free survival rates at 24 and 36 months, defined as from the date of registration to evidence of systemic disease on bone scan or cross-sectional imaging or death, whichever occurs first; (4) safety, feasibility and tolerability of the treatment approach as assessed by NCI Common Toxicity Scales (v3.0); QOL (EPIC survey); and achievement of accrual goals.

Treatment administration

Following registration, docetaxel $70\,\mathrm{mg\,m^{-2}}$ was administered every 3 weeks with prednisone 10 mg per day for four cycles. The dose of docetaxel was slightly decreased owing to reduced docetaxel clearance in this non-castrate setting.[16] Sunitinib was administered at 37.5 mg daily for 14 days followed by a 7-day break every 3 weeks for four cycles out of consistency for this disease state and timing of administration (every 3 weeks) and was the dose evaluated in the phase II and III trials in CRPC. PEG-filgrastim was used on day 2 of each cycle. Following the completion of systemic therapy (on day 84), external beam RT to 66 Gy was administered to the prostate bed only without nodal irradiation over 6–7 weeks (see Figure 1 for schema). RT was initiated starting on day 100–120. No androgen ablation was administered except in the case of PSA progression.

Unacceptable toxicities and dose-limiting toxicities (DLTs) were defined as grade 3 or 4 neutropenia associated with fever or neutropenia lasting 7 days or more and resulting in treatment delay owing to persistent grade >2 neutropenia at the start of the subsequent cycle, or platelets $<50\,000\,\mathrm{mm^{-3}}$ or associated with clinically significant bleeding which is possibly, probably or definitely owing to the study drug; and any grade $\geqslant 3$ non-hematologic toxicity which is possibly, probably or definitely owing to the study drug. Toxicity was monitored using a three-stage design. Two interim analyses were performed after 12 and 24 subjects were enrolled with pre-specified stopping rules based on >5 or 7 DLTs, respectively. The analyses were conducted on the basis of the cumulative total of DLTs that occurred during the treatment interval, including systemic therapy and radiation therapy up to 28 days following completion of radiation therapy.

Patients were assessed for QOL outcomes using the EPIC-short form assessment[17] at baseline, day 1 of cycle 3 of chemotherapy and at 12, 24 and 36 months in follow-up post treatment. PSA was evaluated at baseline, cycle 3 of systemic therapy, before radiation and every 3 months following radiation. Imaging with CT abdomen/pelvis and bone scan was performed on all the patients at baseline and annually for 3 years regardless of PSA results.

Statistical design and data analysis

This study used a single-stage design for efficacy with a target sample size of 38 men, but had two interim safety analyses. Assuming that the PFS rate at 24 months among prostate cancer patients to be 65%, the trial was designed to have 90% power (one-sided type I error rate of 0.10) to reject the null hypothesis of PFS rate of 65% when the true PFS rate at 24 months is 83%. The historic control in this study was based on a model and nomogram by Stephenson *et al.*[1] for men with recurrent disease after RP. This nomogram was used prospectively to estimate the predicted probability of recurrence with salvage EBXRT alone based on the clinical characteristics of the enrolled subjects for the primary comparison.

The Kaplan–Meier product-limit estimator was used to estimate the PFS distribution, metastasis-free survival and local recurrence rates over time. Descriptive statistics were used to address the secondary end points of safety and patient/physician acceptance as measured by accrual time and QOL evaluations. Feasibility was measured through completion of the trial and meeting timely accrual goals. Subjects who withdrew before receiving any of the study intervention on protocol were replaced.

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Table 1. Baseline characteristics ($n = 34$) of the patients in the multimodality trial

Total no. of patients	34
Age, years, median (range)	61.5 (41–74)
Race, total (%)	
White	29 (85)
Black or African American	3 (9)
Native Hawaiian or other Pacific Islander	1 (3)
Asian	1 (3)
Ethnicity, total (%)	
Hispanic or Latino	1 (3)
Not Hispanic or Latino	28 (82)
Not reported	5 (15)
KPS score, total (%)	
90	3 (9)
100	31 (91)
Gleason sum, total (%)	
7	17 (53)
8–10	16 (47)
T stage, total (%)	
T2B	3 (9)
T2C	9 (26)
T3A	9 (26)
T3B	12 (35)
T4A	1 (3)
Extracapsular extension, total (%)	
No	11 (32)
Yes	23 (68)
Positive margins at RP, total (%)	
No	17 (50)
Yes	17 (50)
Seminal vesicle invasion, total (%)	
No	22 (65)
Yes	12 (35)
Lymph node metastases at RP, total (%)	
No	26 (76)
Yes	8 (24)
Persistently elevated PSA after RP, total (%)	
No	8 (24)
Yes	26 (76)
Laboratory values, median (range)	
Serum total testosterone (ng dl^{-1})	290.5 (136.0–848.0)
PSA at trial entry (ng ml^{-1})	0.54 (0.20–2.75)
PSA at radical prostatectomy (ng ml^{-1})	8.30 (3.05–92.00)

Abbreviation: RP, radical prostatectomy.

RESULTS

Patient characteristics

A total of 34 out of a planned 38 subjects were enrolled during this study (Table 1). Eighty-five percent of men were white, 9% black, and the median age was 62 years. Gleason sum of 8–10 adenocarcinoma was present in 47% of men, 64% were surgical stage T3 or higher, 50% were margin positive, 35% had seminal vesicle invasion and 24% were node positive (resected). The median time from surgery to entry was 11 months (range 3–45 months). Seventy-six percent of men had a persistently detectable PSA immediately (after 90 days) after surgery, and the median PSA at study entry was 0.54 ng ml^{-1}. Median follow-up of patients was 37.8 months.

Safety

Enrollment was halted early after 34 patients had accrued owing to an excess number of unacceptable DLTs, with a total of nine DLTs occurring (Table 2). These DLTs were observed after meeting pre-specified safety criteria for continuing after interim analyses at 12 and 24 patients enrolled. These DLTs were observed after the second interim safety analysis and once the pre-specified threshold for unacceptable toxicity was met, further accrual was stopped. However, patients were followed long term for safety and efficacy and the primary and secondary end points. All the toxicities resolved after discontinuation of study drugs, and all the patients went on to receive salvage radiation as planned and were followed for efficacy.

The observed DLTs included grade 4 neutropenia (two events), grade 3 hand–foot syndrome (four events), grade 3 AST elevation (one event), grade 3 diarrhea (one event), grade 3 vomiting (one event) and grade 3 fatigue (one event), all felt to be likely related to the study drug combination (Table 2). A summary of all adverse events in the descending order of frequency is provided in Table 3, in which fatigue, dysgeusia, alopecia, diarrhea, heartburn, nausea, bone pain, hand–foot syndrome, stomatitis, dry skin, watery eyes, anemia, hypertension, onycholysis, rash, anorexia, epistaxis, liver function test elevations, fever, dyspnea and headache were the most common and occurred at $>10\%$ incidence and felt to be at least possibly related to study drugs. Neutropenic fever occurred in $<10\%$, and there were no grade 5 adverse events. Patients who developed toxicity including DLTs were still followed for efficacy.

Efficacy

The estimated 24-month PFS rate was 51% (95% CI = 33–67%; Figure 2, Table 4). As of the last follow-up, the 36-month PFS rate was 48% and the median PFS was 26.2 months (95% CI: 12.5–not reached). Using a nomogram-adjusted data set, we project that the predicted outcomes with radiation alone in our study would have resulted in a 24-month PFS rate of 52% (bootstrapped 95% CI: 45–57%). When analyzed by node-positive status, the 24-month PFS rate for node-negative was 52% (95% CI: 31–70%) and 47% (95% CI: 12–76%) for node-positive men. As of May 2015, 16 progression events have occurred, all biochemical in nature, with no local recurrences or distant metastases preceding PSA relapse, and with only one distant metastasis following PSA relapse.

The median PSA nadir on study was 0.1 ng ml^{-1}, and 33% of men achieved an undetectable PSA following treatment. Before initiating radiation, 70% of men treated with docetaxel and sunitinib experienced a PSA decline, with a median percent decline of 99%. Six men (17.6%) had an undetectable PSA at 2 years. All men who progressed on study ($n = 16$) have subsequently responded to ADT and are in long-term follow-up. There were no deaths on study or during follow-up.

Quality of life

All men completed QOL surveys to assess patient-reported outcomes using the EPIC-short-form assessment over time.[17] A clinically meaningful change is considered to be a 0.5 s.d. change in an EPIC subscale, defined as 9 for urinary irritation, 11 for incontinence, 8 for bowel and 12 for sexual function. The mean baseline scores ($n = 33$ for all surveys except $n = 34$ for urinary incontinence) of urinary irritation, urinary incontinence, bowel function and sexual function domains were 90, 70, 98 and 24 on a 100-point scale, with 100 being perfect function and 0 indicating no function, suggesting a low degree of baseline urinary irritation or bowel dysfunction, but a high level of pre-existing urinary incontinence and sexual dysfunction following radical prostatectomy. Urinary irritation transiently worsened at 12 months ($n = 21$) to a mean score of 86, but largely recovered by 24 months among

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Table 2. DLTs experienced in this trial

CTC category and term	*Grade*
Blood/bone marrow	
Neutropenia (2)	4
Dermatology/skin	
Rash: hand–foot skin reaction (4)	3
Metabolic/laboratory	
AST increase (1)	3
Gastrointestinal	
Diarrhea (1)	3
Vomiting (1)	3
Constitutional symptoms	
Fatigue (asthenia, lethargy) (1)	3

Abbreviation: DLTs, dose-limiting toxicities. Note one patient experienced two DLTs, which counted as one total DLT on a per patient basis for this study per protocol.

Table 3. Adverse events at least possibly related to study drugs by NCI Common Toxicity Criteria v4.0, listed by maximum grade experienced

Toxicity term	*Grade 1,* n *(%)*	*Grade 2,* n *(%)*	*Grade 3,* n *(%)*	*Grade 4,* n *(%)*
Fatigue	23 (68)	6 (18)	2 (6)	0 (0)
Taste alteration (dysgeusia)	27 (79)	1 (3)	0 (0)	0 (0)
Hair loss/alopecia (scalp or body)	24 (71)	2 (6)	0 (0)	0 (0)
Diarrhea	21 (62)	2 (6)	1 (3)	0 (0)
Heartburn/dyspepsia	10 (29)	4 (12)	0 (0)	0 (0)
Nausea	11 (32)	1 (3)	0 (0)	0 (0)
Bone pain	9 (26)	2 (6)	0 (0)	0 (0)
Hand–foot syndrome	2 (6)	4 (12)	4 (12)	0 (0)
Mucositis/stomatitis	7 (21)	2 (6)	0 (0)	0 (0)
Neuropathy: sensory	7 (21)	1 (3)	0 (0)	0 (0)
Dry skin	6 (18)	1 (3)	0 (0)	0 (0)
Watery eye (epiphora, tearing)	5 (15)	1 (3)	0 (0)	0 (0)
Hemoglobin	4 (12)	1 (3)	0 (0)	0 (0)
Hypertension	2 (6)	3 (9)	0 (0)	0 (0)
Nail changes	5 (15)	0 (0)	0 (0)	0 (0)
Rash/desquamation	5 (15)	0 (0)	0 (0)	0 (0)
Anorexia	3 (9)	2 (6)	0 (0)	0 (0)
Epistaxis	5 (15)	0 (0)	0 (0)	0 (0)
ALT, SGPT increase	4 (12)	0 (0)	1 (3)	0 (0)
AST, SGOT increase	3 (9)	1 (3)	1 (3)	0 (0)
Hiccoughs	5 (15)	0 (0)	0 (0)	0 (0)
Neutrophils/granulocytes (ANC/AGC)	0 (0%)	0 (0)	0 (0)	4 (12)
Non-neutropenic fever	4 (12)	0 (0)	0 (0)	0 (0)
Headache	4 (12)	0 (0)	0 (0)	0 (0)
Dyspnea	4 (12)	0 (0)	0 (0)	0 (0)
Nasal cavity/paranasal sinus reactions	4 (12)	0 (0)	0 (0)	0 (0)
Urinary frequency/urgency	3 (9)	1 (3)	0 (0)	0 (0)
Hyperglycemia	0 (0)	2 (6)	1 (3)	0 (0)
Pain: oral cavity	1 (3)	0 (0)	1 (3)	0 (0)
Vomiting	1 (3)	0 (0)	1 (3)	0 (0)
Thrombosis/thrombus/ embolism	0 (0)	0 (0)	1 (3)	0 (0)
Leukocytes (total WBC)	0 (0)	0 (0)	0 (0)	1 (3)
Cholecystitis	0 (0)	0 (0)	1 (3)	0 (0)
Pneumonia	0 (0)	0 (0)	1 (3)	0 (0)

Abbreviation: WBC, white blood cell. There were no grade 5 toxicities.

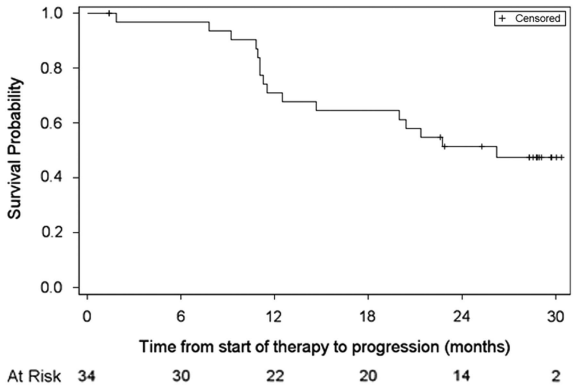

Figure 2. Kaplan–Meier estimate of progression-free survival in this study.

evaluable patients who completed the survey (mean score of 90, $n = 10$). For urinary incontinence, improvements were seen by 12 months (mean score 74), but returned to baseline (mean score of 70) by 24 months. Bowel function remained stable and at a high level throughout all time points (means of 93 at 12 months, 92 at 24 months), while sexual function remained low at all time points (means of 29 at 12 months, 33 at 24 months). Figure 3 presents the patient QOL profile over time for individual domains and the regression line (red) summarizing the group changes over time.

DISCUSSION

We found that while the combination of sunitinib and docetaxel followed by salvage external beam RT was unacceptably toxic in this patient population of otherwise healthy men with aggressive prostate cancer and a rising PSA following radical prostatectomy, long-term disease control was observed. In this trial, over half of the men treated with this multimodality approach were free of disease progression at 24–36 months. However, based on the similar efficacy observed as compared with nomogram-adjusted historic data with radiation alone, this combination cannot be justified for further development. Thus, we have provided evidence using an intermediate surrogate end point that development of docetaxel and sunitinib in a phase 3 salvage RT setting is not warranted.

At the time that this multimodality trial was conceived, sunitinib was under development in combination with docetaxel for men with mCRPC as well as in phase 3 testing as a single agent in the post-docetaxel mCRPC setting. Although the single agent trial led to a nearly 30% improvement in PFS over time, no statistically significant improvement in overall survival was observed.[13] This, combined with the failures of other antivascular endothelial growth factor targeted approaches to improve survival such as bevacizumab, sunitinib or aflibercept (vascular endothelial growth factor trap) in men with mCRPC, have limited the enthusiasm for these agents in men with CRPC.[13,18,19] However, the activity of these agents in earlier stages of the disease has been unknown, and given the synergy observed preclinically and clinically with sunitinib and docetaxel, this trial sought to address this question. In addition, recent successful trials of early docetaxel use in hormone-sensitive men with locally advanced and metastatic prostate cancer suggest that docetaxel is worthy of evaluation in the non-metastatic PSA recurrent setting.[20–22] For example, in RTOG 0521, adjuvant docetaxel following radiation/ADT led to suggestions of improved 4-year survival in men with high-risk localized prostate cancer, whereas in STAMPEDE and CHAARTED, a robust survival benefit of 13–22 months was observed with induction docetaxel (six cycles every 3 weeks) and ADT over

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Table 4. Primary efficacy end points over time in overall population and according to resected nodal stage

	No. failed	*Median PFS months (95% CI)*	*6-month PFS rate (95% CI)*	*12-month PFS rate (95% CI)*	*16-month PFS rate (95% CI)*	*Primary end point: 24-month PFS rate (95% CI)*
Total number of men						
34	16	26.2 (12.5, NE)	96.8% (79.2%, 99.5%)	71% (51.6%, 83.7%)	64.5% (45.2%, 78.5%)	51.4% (32.8%, 67.2%)
Lymph node metastasis status						
No ($n=26$)	11	NE	100% (NE, NE)	74% (51, 87%)	65% (42, 81%)	52% (31, 70%)
Yes ($n=8$)	5	22.7 (2, NE)	88% (39, 98%)	63% (23, 86%)	63% (23, 86%)	47% (12, 76%)

Abbreviations: CI, confidence interval; NE, not estimable; PFS, progression-free survival.

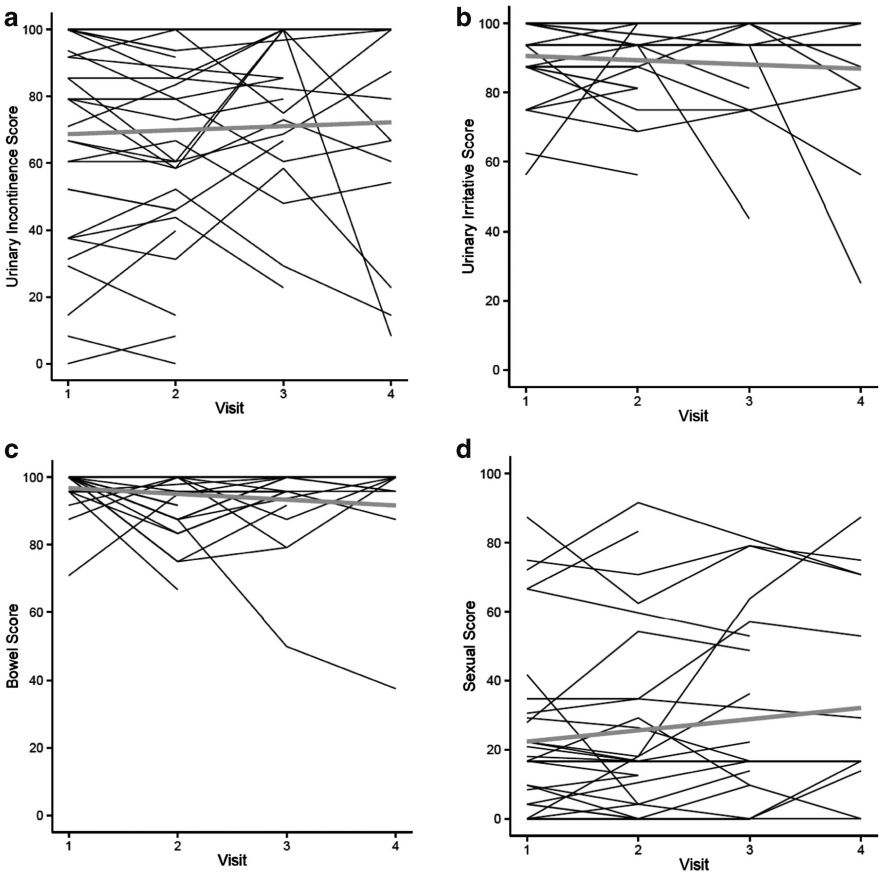

Figure 3. EPIC-SF quality-of-life domain scores over time including (**a**) urinary irritative symptoms, (**b**) urinary incontinence symptoms, (**c**) bowel symptoms and (**d**) sexual function. The red line indicates the regression composite of all subjects at each time point. Note that higher scores reflect higher function on a 0–100 scale. Visit 1 indicates baseline post-radical prostatectomy and before the start of systemic therapy; visit 2 occurs at cycle 3 day 1 of chemotherapy; visit 3 occurs at 12 months following enrollment, ~6 months following the completion of radiation therapy; visit 4 occurs at 24 months following enrollment, ~18 months following the completion of radiation therapy. EPIC-SF, EPIC short form.

ADT alone for men with metastatic castrate-sensitive prostate cancer.[20–22] Our data do not exclude a possible favorable impact of docetaxel with ADT in this salvage setting, but perhaps suggest that a longer course of treatment (that is, six cycles instead of four) may be required.

Among the men enrolled, nearly 25% had node-positive resected disease, and the majority of patients had Gleason 8–10 and pT3 disease at surgery. Our 24-month outcomes, however, are similar to those expected from the Stephenson nomogram with radiation ± ADT alone, suggesting that the docetaxel and sunitinib were not sufficiently active to improve long-term outcomes in these patients, and sufficiently toxic that we cannot recommend this strategy in future trials in these patients. These data are consistent with a recent trial of docetaxel and ADT in the non-metastatic PSA recurrent setting (TAX3503), in which docetaxel only modestly delayed PSA progression.[23]

Toxicities observed with this combined modality approach were not unexpected, despite the frequency and severity of

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unacceptable toxicities. Side effects in all cases were reversible and did not lead to any complications during radiation therapy. Our QOL data suggest transient worsening in urinary irritative symptoms at 12 months post treatment, returning to baseline by 24 months. However, these QOL data are limited by the low number of completed surveys at 24 months, which may bias these data if survey respondents were more likely to have improved QOL as compared with non-respondents. No major changes in patient-reported outcomes for bowel toxicity or urinary incontinence or sexual activity were noted, however, suggesting the overall long-term safety of this approach. Our approach of using a non-ADT-based systemic therapy regimen avoided the adverse effects of ADT; however, based on the lack of clear efficacy, we cannot recommend this combination approach for further study.

One of the successful aspects of this trial was the ability to accrue and complete a combined modality trial that involved both urologic, medical and radiation oncologists across multiple institutions, and in providing a go–no go decision based on a reasonably small number of men and using an intermediate end point. This approach limits the exposure of potentially toxic agents in larger trials, and permits a more rapid decision-making process for drug development in this setting. This collaborative effort was possible through interdisciplinary dialog, intensive screening of clinics by study coordinators and regular discussions among the specialists and faculty to promote referrals and collaborative care and safety oversight, and demonstrated the feasibility of this approach.

Although the present systemic therapies did not lead to improved outcomes, trials evaluating other novel systemic agents may be successfully performed in this high-risk treatment space. Salvage radiation is commonly used instead of adjuvant radiation, given the concerns over the need to commit to radiation and its toxicities when the PSA is undetectable. While the failure rate in the salvage setting remains unacceptably high typically owing to systemic rather than local failure, combined modality approaches may improve upon this. Two such trials are RTOG 9601 investigating long-term bicalutamide at high doses with salvage radiation and RTOG 0534 investigating the role of short-term ADT or pelvic RT (NCT00002874 and NCT00567580). A third trial (GETUG-AFU 16) was recently reported as demonstrating a significantly improved PFS with 6 months of ADT in addition to salvage RT in 743 men in this setting, suggesting that hormonal therapy should be considered a standard practice in the salvage RT setting (NCT00423475).[24] In addition, salvage radiation combined with ADT and enzalutamide or enzalutamide alone are presently under prospective clinical evaluation (NCT02057939 and NCT02203695). Thus, efforts are ongoing with alternative systemic strategies designed to improve cure rates in this setting through this multidisciplinary approach and utilizing early intermediate efficacy end points.

CONFLICT OF INTEREST

This work has received research support from Pfizer and Sanofi (AJA, DJG), consulting with Pfizer and Sanofi (AJA, DJG, MAC), speaker's bureau for Sanofi (DJG). The remaining authors declare no conflict of interest.

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