VOLUME 34 · NUMBER 22 · AUGUST 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized, Double-Blind, Placebo-Controlled Phase III Study of Tasquinimod in Men With Metastatic Castration-Resistant Prostate Cancer

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Published online ahead of print at www.jco.org on June 13, 2016.

Supported by Active Biotech.

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Presented in part at the European Cancer Congress 2015, Vienna, Austria, September 25-29, 2015.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Contributions are found at the end of this article.

Clinical trial information: NCT01234311.

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0732-183X/16/3422w-2636w/$20.00

DOI: 10.1200/JCO.2016.66.9697

ABSTRACT

Purpose

Tasquinimod, a novel oral therapy targeting the tumor microenvironment, significantly improved progression-free survival (PFS) in a randomized, placebo-controlled phase II trial in men with metastatic castration-resistant prostate cancer (mCRPC). This phase III study was conducted to confirm the phase II results and to detect an overall survival (OS) benefit.

Patients and Methods

Men with chemotherapy-naïve mCRPC and evidence of bone metastases were assigned (2:1) to receive tasquinimod once per day or placebo until progression or toxicity. The primary end point was radiographic PFS (rPFS; time from random assignment to radiologic progression or death) per Prostate Cancer Working Group 2 criteria and RECIST 1.1. The study had 99.9% power to detect an rPFS hazard ratio (HR) of 0.6 with a two-sided alpha error of .05 and 80% power to detect a target HR of 0.8 for OS, the key secondary end point.

Results

In all, 1,245 patients were randomly assigned to either tasquinimod (n = 832) or placebo (n = 413) between March 2011 and December 2012 at 241 sites in 37 countries. Baseline characteristics were balanced between groups: median age, 71 years; Karnofsky performance status ≥ 90%, 77.3%; and visceral metastases, 21.1%. Estimated median rPFS by central review was 7.0 months (95% CI, 5.8 to 8.2 months) with tasquinimod and 4.4 months (95% CI, 3.5 to 5.5 months) with placebo (HR, 0.64; 95% CI, 0.54 to 0.75; $P < .001$). Median OS was 21.3 months (95% CI, 19.5 to 23.0 months) with tasquinimod and 24.0 months (95% CI, 21.4 to 26.9 months) with placebo (HR, 1.10; 95% CI, 0.94 to 1.28; $P = .25$). Grade ≥ 3 adverse events were more frequent with tasquinimod (42.8% *v* 33.6%), the most common being anemia, fatigue, and cancer pain.

Conclusion

In chemotherapy-naïve men with mCRPC, tasquinimod significantly improved rPFS compared with placebo. However, no OS benefit was observed.

J Clin Oncol 34:2636-2643. © 2016 by American Society of Clinical Oncology

INTRODUCTION

Treatment options for metastatic castration-resistant prostate cancer (mCRPC) have expanded with the introduction of several new agents that delay disease progression and improve overall survival (OS). These include second-generation androgen-directed therapies, radium-223, sipuleucel-T, and the taxanes cabazitaxel and docetaxel. Despite these advances, mCRPC remains incurable, and survival benefits typically achieved with newer agents are modest while resistance remains common.[1-7] New agents with alternative mechanisms of action that further improve survival while minimizing toxicity are needed.

The tumor microenvironment is increasingly recognized as playing a major role in the formation and growth of metastases.[8] In addition, the host microenvironment has been shown to promote prostate cancer invasion, systemic spread, bone

colonization, and osteoblastic metastasis.[9] Drugs that target the tumor microenvironment therefore offer a potentially new approach in the treatment of advanced prostate cancer.[10] Tasquinimod (ABR-215050; Active Biotech, Lund, Sweden) is an oral immunotherapy with demonstrated effects on the tumor microenvironment that counteract tumor growth.[11,12] One molecular target of tasquinimod is the immunomodulatory protein S100A9, which plays a role in the accumulation and function of innate immune cells, specifically regulatory myeloid cells.[11-13] Targeting regulatory myeloid cells within the tumor microenvironment leads to decreased immune suppression and angiogenesis and prevention of metastasis development. Tasquinimod may also reduce angiogenesis by downregulation of HIF1-controlled genes via interaction with histone deacetylases.[14]

In a randomized, placebo-controlled phase II study in men with mCRPC, tasquinimod significantly improved progression-free survival (PFS; median, 7.6 *v* 3.3 months; hazard ratio [HR], 0.57; $P < .01$).[15] In long-term follow-up, multivariate analysis indicated that the PFS improvement may be associated with improved OS, particularly in patients with bone metastases.[16] The objective of this phase III study was to confirm the benefit of tasquinimod in delaying disease progression and improving OS in men with mCRPC.

PATIENTS AND METHODS

Patients

Eligible patients had histologically confirmed prostate adenocarcinoma with evidence of bone metastases, serum testosterone ≤ 50 ng/dL, disease progression (increasing serum prostate-specific antigen [PSA] as defined by the Prostate Cancer Working Group 2 [PCWG2],[17] progression of soft tissue metastasis, or bone disease progression), and Karnofsky performance status ≥ 70%. Concurrent use of luteinizing hormone-releasing hormone agonists or antagonists and bone agents (denosumab or bisphosphonates) was permitted.

No cytotoxic chemotherapy within 2 years or previous anticancer therapy within 4 weeks (2 weeks for sipuleucel-T) of random assignment was allowed. Prior enzalutamide or abiraterone was permitted. Other exclusion criteria included presence of prostate cancer pain requiring opiate analgesics, systemic exposure to ketoconazole, and ongoing corticosteroid treatment equivalent to a prednisolone or prednisone dose of > 10 mg/day.

Study Design

This multinational, randomized, double-blind, placebo-controlled phase III study was conducted at 241 sites in 37 countries (Appendix Table A1, online only). Patients were randomly assigned in a 2:1 ratio to receive tasquinimod or placebo by using an interactive voice response system. Random assignment was stratified by Karnofsky performance status (≥ 90% *v* < 90%), presence or absence of visceral disease (all metastatic soft tissue except lymph nodes and local recurrence), and geographic region (North America, Europe, the Middle East, Africa, Asia-Pacific, and Latin America). Tasquinimod or placebo was administered orally at a starting dose of 0.25 mg/day for at least 2 weeks.[18] If tolerability was established, the dose was escalated to 0.5 mg/day for 2 weeks and then to 1 mg/day. Patients unable to tolerate the escalated doses could continue in the study at their maximum tolerated dose. Treatment continued until symptomatic disease progressed so that it required alternative antitumor therapy or until poor tolerability occurred. After the end of treatment, patients continued follow-up with visits every 3 months until death or until 727 patients had reached the survival end point.

The study was approved by the institutional review boards or ethics committees at each participating center and was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before study entry.

End Points

The primary end point was radiographic PFS (rPFS), the time from random assignment to radiologic progression or death, whatever the cause. Radiographic progression was defined as soft tissue progression (RECIST 1.1),[19] bone progression detected with confirmatory bone scans (PCWG2),[7] or radiographically confirmed spinal cord compression or fracture as a result of malignant progression. Soft tissue lesions were evaluated by computed tomography or magnetic resonance imaging scans by the investigator. All scans underwent independent central review, with reviewers blinded to study treatment and investigator assessments.

The key secondary end point was OS, defined as time from random assignment to death. Other prespecified secondary end points included time to radiologic progression, time to symptomatic progression, time to PSA progression, time to initiation of further cytotoxic therapy, time to opiate use, and time to deterioration of quality-of-life (QoL) measure (Functional Assessment of Cancer Therapy-Prostate [FACT-P]). Safety was assessed on the basis of physical examination, vital signs measurements, clinical laboratory analyses, and adverse events (AEs; coded using Medical Dictionary for Regulatory Activities [MedDRA]; graded using Common Terminology Criteria for Adverse Events [CTCAE] version 4.0).

Statistical Analysis

The planned sample size of 1,200 patients (800 in the tasquinimod arm and 400 in the placebo arm) provided 99.9% power at a two-sided significance level of 0.05 to detect an HR of 0.6 for the primary end point of rPFS, corresponding to an increase in median PFS from 3.4 to 5.7 months. The study was also designed to detect an HR of 0.8 for the key secondary end point of OS, corresponding to an increase in median OS from 22 to 27.5 months. Specifying a two-sided significance level of 0.05, the study had 80% power to detect the OS difference after 727 deaths had been observed. The OS end point comparisons incorporated group sequential design involving two interim analyses (at 473 and 582 events) and a final analysis at 727 events using O'Brien-Fleming stopping boundaries[20]: first interim analysis, $P \leq .0109$; second interim analysis, $P \leq .0212$; and final analysis, $P \leq .0422$. rPFS was analyzed at the first planned interim analysis for OS (after 473 events). If the comparison of rPFS reached statistical significance ($P \leq .05$), the first comparison of OS was performed; however, the results were not reported until the final analysis.

A stratified log-rank test by factors at random assignment was used to compare rPFS, OS, and the time-to-event secondary end points for tasquinimod versus placebo (analysis of PSA doubling time was not stratified). To describe time-to-event variables, Kaplan-Meier curves and life tables by treatment group were generated, and CIs were calculated.[21] Patients who did not experience an event were censored at the date of their last adequate assessment, previous assessment, last visit, or death, depending on the end point and analysis. Treatment effect was estimated by calculating the HR and its 95% CI from a Cox proportional hazards model stratified by factors at random assignment. For rPFS and OS, Cox proportional hazards models were performed for predefined subgroups and multivariate analyses. In the latter analyses, after testing each prespecified prognostic factor with a univariate analysis, a backward selection approach was used. Treatment was always included in the models.

All efficacy end points were analyzed by planned treatment in the intent-to-treat population (all randomly assigned patients, regardless of whether any study treatment dosing was completed). The safety analysis population comprised all patients who received at least one dose of study treatment. Safety was analyzed according to treatment received. All statistical analyses were performed by using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patient Disposition

Of 1,645 patients screened, 1,245 were randomly assigned to receive tasquinimod (n = 832) or placebo (n = 413) between March 29, 2011, and December 7, 2012 (Appendix Table A1). Two patients from each group did not receive treatment after random assignment (Fig 1). Baseline characteristics were generally well balanced between the groups (Table 1). A greater proportion of patients in the tasquinimod group had higher levels of baseline tumor pain (Visual Analog Scale > 4: 18.6% *v* 14.5%). Median time since diagnosis was shorter in the tasquinimod group than in the placebo group (45.7 *v* 57.7 months).

At final analysis (cutoff date: February 13, 2015), median follow-up was 30.0 months in the tasquinimod arm and 30.7 months in the placebo arm, and 96.1% of patients had discontinued treatment. The most common reasons for discontinuation (tasquinimod *v* placebo) were radiographic progression (23.8% *v* 36.5%), symptomatic progression requiring new anticancer therapy (21.3% *v* 18.8%), and poor tolerability or AEs (17.9% *v* 8.8%; Fig 1).

Efficacy

The final analysis of the primary end point of rPFS was performed at the time of the first interim analysis of OS. Radiographic progression by central review, or death, occurred in 396 patients (48%) in the tasquinimod group and in 258 patients (62%) in the placebo group. Estimated median rPFS was 7.0 months (95% CI, 5.8 to 8.2 months) for tasquinimod and 4.4 months (95% CI, 3.5 to 5.5 months) months for placebo, corresponding to a 36% reduction in the risk of radiographic progression or death with tasquinimod versus placebo (HR, 0.64; 95% CI, 0.54 to 0.75; $P < .001$; Fig 2A). Similar results were seen in the assessment by local review: estimated median rPFS was 5.7 months (95% CI, 5.5 to 6.2 months) and 4.1 months (95% CI, 3.1 to 5.1 months), respectively (HR 0.69; 95% CI, 0.60 to 0.80; $P < .001$).

OS results were not significant at either of the two interim analyses and, because no safety concerns were raised, the Data and Safety Monitoring Board recommended continuation of the study according to the protocol. At final analysis of OS, 492 deaths (59.1%) had occurred in the tasquinimod group and 238 deaths (57.6%) had occurred in the placebo group. Tasquinimod did not improve OS compared with placebo (median OS, 21.3 months [95% CI, 19.5 to 23.0 months] with tasquinimod and 24.0 months [95% CI, 21.4 to 26.9 months] with placebo; HR, 1.10; 95% CI, 0.94 to 1.28; $P = .25$; Fig 2B). The rPFS and OS results were consistent when examined across predefined patient subgroups without evidence of significant heterogeneity (Fig 3).

In general, secondary end points that favored tasquinimod over placebo included the radiographic- and PSA-based outcomes (Table 2 and Appendix Table A2, online only). In contrast, symptomatically assessed end points, such as time to symptomatic progression, time to opiate use, and deterioration in QoL, favored placebo. Time to initiation of salvage therapy was longer with tasquinimod than with placebo (11.4 *v* 8.1 months; $P = .001$), as was time to initiation of further cytotoxic therapy (25.8 *v* 16.0 months; $P = .021$).

One quarter of patients (315 [25.3%] of 1,245) had undergone orchiectomy, and most patients (1,178 [94.6%] of 1,245) had received hormonal therapy pre-enrollment (mostly bicalutamide, flutamide, and luteinizing hormone-releasing hormone analogs). In contrast, only a few patients had received prior abiraterone (five patients [0.6%] in the tasquinimod group *v* seven patients [1.7%] in the placebo group) or enzalutamide (zero *v* one [0.2%]). These treatments were more commonly

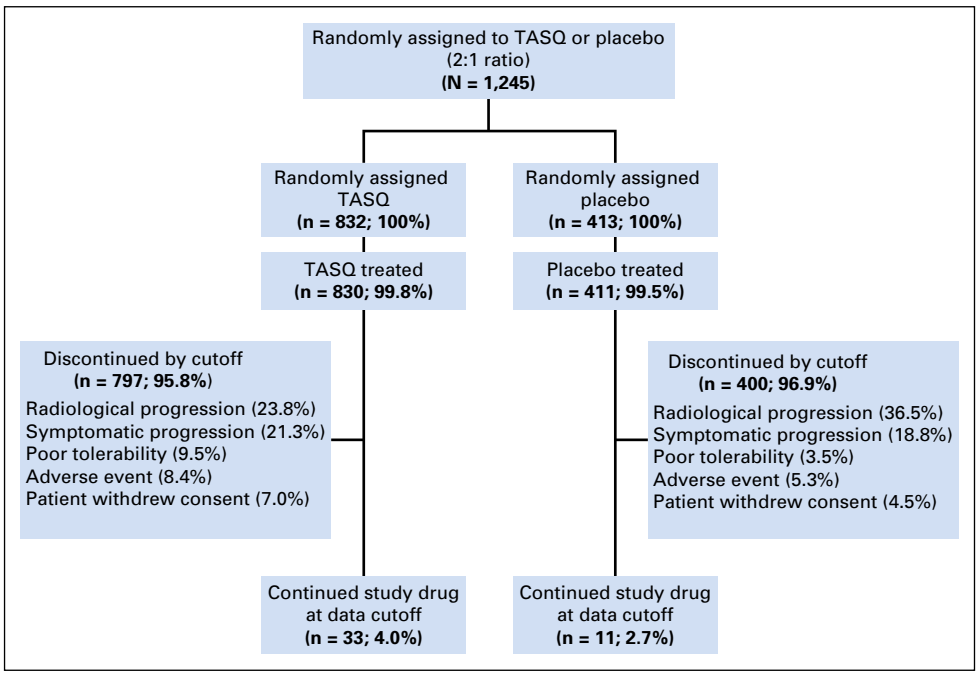

Fig 1. CONSORT diagram. TASQ, tasquinimod.

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Tasquinimod (n = 832) No.	%	Placebo (n = 413) No.	%
Median age, years (range)	71.0 (43-92)		71.0 (48-92)	
Age group (years)				
≤ 65	214	25.7	106	25.7
66-75	371	44.6	186	45.0
76-80	144	17.3	64	15.5
> 80	103	12.4	57	13.8
Race*				
White	729	87.6	359	86.9
Black	20	2.4	8	1.9
Asian	46	5.5	27	6.5
Other	37	4.4	18	4.4
Ethnicity				
Hispanic/Latino	97	11.7	42	10.2
Non-Hispanic/Latino	735	88.3	371	89.8
Median time since diagnosis, months (range)	45.7 (0.1-299.6)		57.7 (0.3-319.9)	
Karnofsky performance status†				
< 90%	187	22.5	95	23.0
≥ 90%	645	77.5	318	77.0
Geographic region of enrollment†				
North America	143	17.2	72	17.4
Europe/Middle East/ Africa	505	60.7	254	61.5
Asia-Pacific	94	11.3	46	11.1
Latin America	90	10.8	41	9.9
Tumor pain (VAS)‡				
0	371	44.6	195	47.2
1-3	286	34.4	157	38.0
4-10	155	18.6	60	14.5
Median PSA, μg/L (range)	54.3 (0.6-8,710.7)		50.1 (0.2-5,679.5)	
Gleason score of 8 to 10 at diagnosis	398	47.8	190	46.0
Visceral disease present†	176	21.2	87	21.1
Location of metastases				
Visceral§	161	19.4	76	18.4
Bone	824	99.0	409	99.0
Node	297	35.7	179	43.3
No. of bone metastases				
< 10	377	45.3	194	47.0
≥ 10	447	53.7	215	52.1
Previous second-generation hormonal therapy¶	65	7.8	48	11.6

Abbreviations: PSA, prostate-specific antigen; VAS, Visual Analog Scale.
*Data missing for one patient in the placebo group.
†According to interactive voice response system data, except for Europe, Middle East, and Asia-Pacific subcategories for geographic region.
‡Data missing for 20 patients in the tasquinimod group and one patient in the placebo group.
§According to electronic case report form data. Indicated location does not exclude other sites.
¶Abiraterone, enzalutamide, ketoconazole, or any other second-generation hormonal treatment.

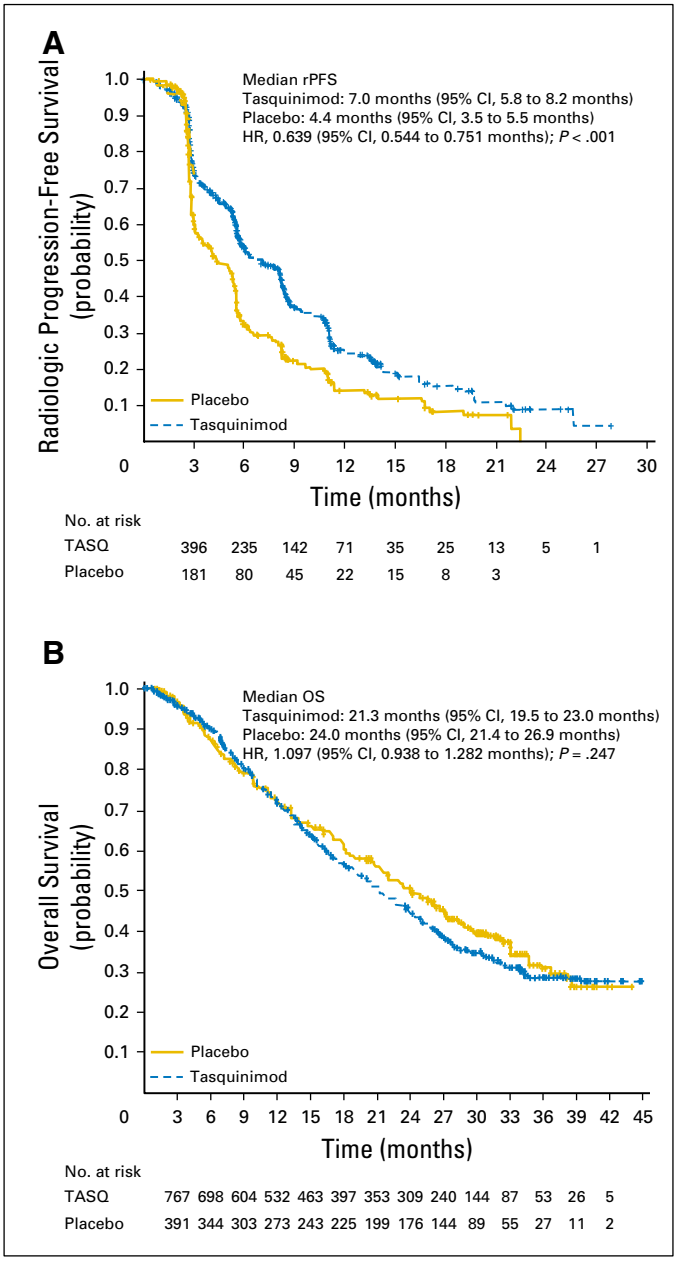

Fig 2. Kaplan-Meier analysis of (A) radiologic progression-free survival (rPFS; central review) and (B) overall survival (OS). HR, hazard ratio; TASQ, tasquinimod.

available during the follow-up period after withdrawal from study treatment and were used more in the placebo group (abiraterone, 209 [25%] *v* 127 [31%]; enzalutamide, 66 [8%] *v* 48 [12%]). More than one third of patients received docetaxel after the study (281 [34%] *v* 166 [40%]).

Drug Exposure and Safety

Overall median treatment duration was 137 days (range, 1 to 1,377 days) for tasquinimod and 133 days (range, 8 to 1,179 days) for placebo, and most patients (82% and 92%, respectively) escalated to the maximum dose of 1 mg/day.

The proportion of patients with at least one dose reduction from maximum dose was higher in the tasquinimod group than in the placebo group (17.5% *v* 5.6% for the 1 mg/day dose and 1.4% *v* 0% for the 0.5 mg/day dose). The majority of patients in both treatment groups experienced at least one treatment-emergent AE (Table 3). A greater proportion of patients in the tasquinimod group discontinued treatment because of AEs (17.7% *v* 10.2%), mainly as a result of decreased appetite, fatigue, asthenia, or nausea.

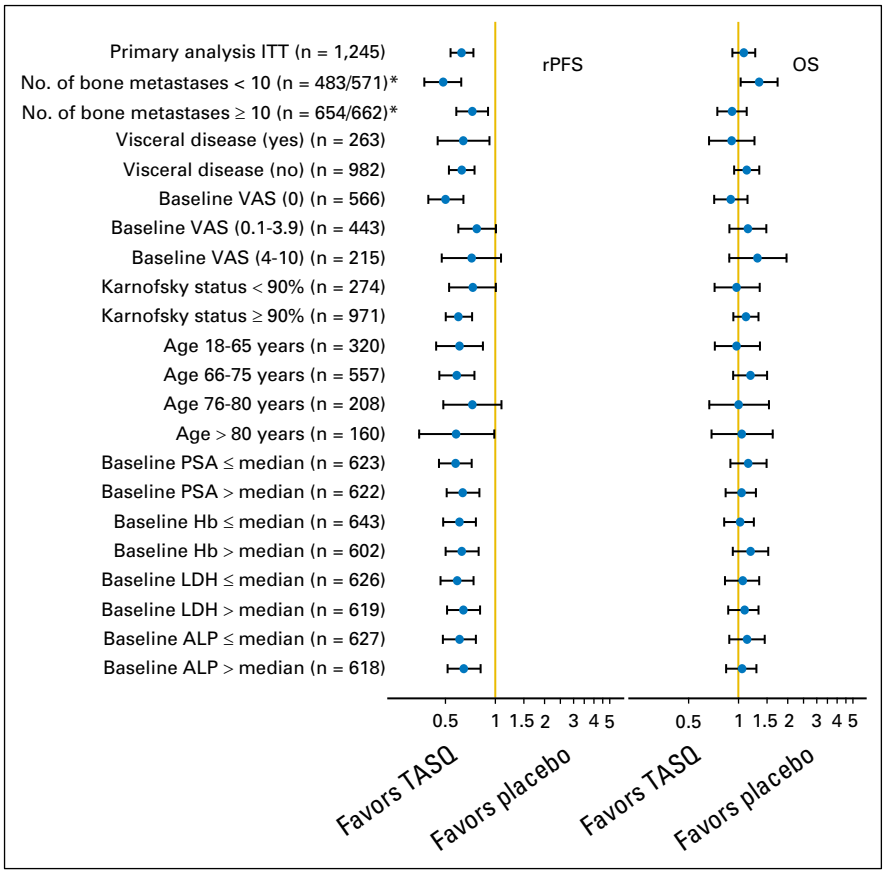

Fig 3. Radiologic progression-free survival (rPFS) and overall survival (OS) outcomes in patient subgroups. *Number of patients included in analyses of rPFS/OS. ALP, alkaline phosphatase; Hb, hemoglobin; ITT, intent to treat; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; TASQ, tasquinimod; VAS, Visual Analog Scale.

The most common reported AEs were GI disorders (60.2% for the tasquinimod group *v* 47.9% for the placebo group), general disorders and administration site conditions (55.1% *v* 39.9%), and musculoskeletal and connective tissue disorders (48.2% *v* 36.7%). The most frequently reported AEs are summarized in Table 3.

A total of 229 patients (27.6%) in the tasquinimod group and 97 patients (23.6%) in the placebo group experienced at least one serious AE, the most common being renal and urinary disorders (7.3% *v* 7.3%), infections and infestations (5.1% *v* 4.1%), and blood and lymphatic system disorders (4.3% *v* 4.1%).

Table 2. Secondary Efficacy End Points

	Tasquinimod (n = 832)		Placebo (n = 413)				
Progression	Median (months)	95% CI	Median (months)	95% CI	HR	95% CI	*P*
Radiologic progression							
Local	8.0	5.8 to 8.3	4.6	3.2 to 5.5	0.683	0.591 to 0.789	< .001
Central	8.4	8.1 to 9.2	5.5	4.5 to 5.6	0.628	0.534 to 0.739	< .001
Soft tissue progression (RECIST 1.1)							
Local	16.6	13.6 to 19.4	8.3	5.9 to 10.9	0.586	0.483 to 0.711	< .001
Central	16.6	14.6 to 20.5	11.1	8.2 to 14.0	0.621	0.504 to 0.765	< .001
Symptomatic progression*	9.5	7.8 to 11.1	11.9	8.9 to 14.1	1.171	1.014 to 1.353	.031
Initiation of salvage therapy†	11.4	9.1 to 13.1	8.1	6.7 to 9.7	0.778	0.667 to 0.907	.001
Initiation of further cytotoxic therapy	25.8	22.1 to 35.9	16.0	13.6 to 23.2	0.809	0.675 to 0.969	.021
Opiate use for cancer pain	29.5	25.1 to NR	35.9	29.4 to NR	1.328	1.060 to 1.664	.013
FACT-P deterioration (criterion 1)‡	3.0	2.9 to 3.3	5.8	5.6 to 6.5	1.447	1.265 to 1.655	< .001
PSA progression	2.9	2.8 to 2.9	2.8	2.8 to 2.8	0.826	0.723 to 0.945	.003

NOTE. Time to skeletal-related events and time to symptomatic progression as a result of skeletal-related events could not be calculated because of the low number of events.
Abbreviations: FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; NR, not reached; PSA, prostate-specific antigen.
*Including death as a result of prostate cancer.
†Including radionuclide, chemotherapy, or radiation therapy.
‡Deterioration event was classified as the first of (1) death as a result of prostate cancer, (2) significant and meaningful decline in FACT-P total score, or (3) disease progression, defined as radiologic progression and a missing FACT-P at the same scheduled visit.

Table 3. Most Common AEs Occurring in at Least 5% of Patients in Either Treatment Group

	Tasquinimod (n = 830)				Placebo (n = 411)			
	All Grades		Grades 3 to 5		All Grades		Grades 3 to 5	
AE	No.	%	No.	%	No.	%	No.	%
All AEs	791	95.3	355	42.8	381	92.7	138	33.6
Cancer pain	264	31.8	27	3.3	129	31.4	10	2.4
Decreased appetite	250	30.1	15	1.8	67	16.3	4	1.0
Nausea	222	26.7	7	0.8	89	21.7	3	0.7
Fatigue	217	26.1	28	3.4	72	17.5	9	2.2
Constipation	194	23.4	8	1.0	67	16.3	2	0.5
Anemia	179	21.6	69	8.3	67	16.3	31	7.5
Asthenia	140	16.9	23	2.8	51	12.4	8	1.9
Decreased weight	125	15.1	15	1.8	35	8.5	3	0.7
Back pain	105	12.7	10	1.2	38	9.2	1	0.2
Pain in extremity	104	12.5	10	1.2	31	7.5	1	0.2
Arthralgia	101	12.2	8	1.0	52	12.7	0	
Diarrhea	94	11.3	3	0.4	42	10.2	3	0.7
Insomnia	87	10.5	2	0.2	30	7.3	0	
Vomiting	87	10.5	3	0.4	28	6.8	3	0.7
Peripheral edema	85	10.2	3	0.4	28	6.8	1	0.2

Abbreviation: AE, adverse event.

The incidence of vascular disorders was similar for the tasquinimod and placebo groups (12.4% *v* 13.1%), as was the incidence of deep vein thrombosis (0.7% *v* 1.5%). Cardiac disorders were more frequent with tasquinimod (all grades, 10% *v* 6.8%; grades 3 to 5, 3.4% *v* 1.6%; serious AEs, 3.9% *v* 1.9%). The frequencies of specific cardiac events for tasquinimod and placebo groups, respectively, were atrial fibrillation (2.8% *v* 0.7%), angina pectoris (1.2% *v* 0.7%), cardiac failure (1.2% *v* 0.2%), pericardial effusion (0.8% *v* 0%), pericarditis (0.4% *v* 0%), coronary artery disease (0.4% *v* 0%), and myocardial infarction (0.5% *v* 0.2%). The incidence of death as a result of AEs was similar between the groups: 27 patients (3.3%) in the tasquinimod group and 15 patients (3.6%) in the placebo group. There were four (0.5%) cardiac AE-related deaths in the tasquinimod group and one (0.2%) in the placebo group.

DISCUSSION

Tasquinimod was shown in a randomized phase II study to improve PFS in patients with mCRPC, and it was further indicated that this effect might be associated with an OS benefit.[15,16] The primary objective of this phase III study was to confirm the phase II findings, and therefore a similar design was used with rPFS as the primary end point. However, the study was designed with sufficient statistical power to detect a potential OS benefit, and OS was the main secondary end point. The results showed that rPFS was significantly delayed by tasquinimod (36% reduced risk of radiographic progression or death *v* placebo, by central review; HR, 0.64), thereby confirming the phase II findings. There was good agreement between independent radiologists and local investigator assessment, suggesting that rPFS can be reliably ascertained, and recent data suggest that delays in rPFS may be associated with prolonged survival.[22]

However, the significant rPFS benefit with tasquinimod did not translate into improved survival over time. Subgroup analyses demonstrated consistent results for rPFS and OS and did not highlight any clear heterogeneity for an OS benefit among any of the subgroups. Tasquinimod seemed to provide clinical benefit over placebo with respect to a number of other objective radiology-based measures as well as for time to PSA progression. Time to initiation of further cytotoxic therapy was prolonged by 9.8 months likely because of the delayed progression with tasquinimod treatment. However, this was not the case for more subjective outcomes such as time to opiate use for cancer pain, time to tumor-related pain progression, and time to QoL deterioration, all of which were better in the placebo group. The most common AEs over-represented in the tasquinimod group included the types of events that are also commonly seen as signs of cancer progression and general health deterioration and thus may have contributed to the unfavorable outcome of symptomatically assessed end points.

Assessing clinical benefit in mCRPC is challenging, given the heterogeneous nature of the disease and differential effects of subsequent therapy on traditional end points, such as OS and postprogression time-to-event end points.[23] PCWG2 guidelines on defining disease progression[7] have been adopted as the standard primary efficacy measure in most recent clinical trials in mCRPC, and there is widespread interest in the use of PCWG2-defined rPFS as a surrogate end point of survival benefit. A recent analysis of the phase III COU-AA-302 (Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer) trial demonstrated a significant correlation between rPFS and OS.[22] However, the lack of correlation between rPFS and OS in this study and in other phase III studies in mCRPC[24-26] illustrates that significant improvements in rPFS may not always translate into longer-term survival benefit.

Among several possible explanations for the lack of OS benefit in this study, one contributory factor may be the availability of more effective salvage therapies that prolong OS treatment after the study,[27] many of which were not widely available at the time of the phase II study. The current availability of such agents (eg, abiraterone and enzalutamide) may have had an impact on the course of disease because patients in the placebo group gained access before those in the tasquinimod group on account of their earlier withdrawal from study treatment. Indeed, post-treatment use of abiraterone and enzalutamide was more common among patients in the placebo group. Furthermore, baseline characteristics suggest a more aggressive cancer population in the tasquinimod arm as indicated by an imbalance in median time since diagnosis and baseline Visual Analog Scale score for tumor-related pain. It may also be that the survival results were influenced by a combination of the relatively modest effect on rPFS and other confounding factors, suggesting that tasquinimod may not have sufficient efficacy as a single agent to have an impact on long-term OS.

Further study of predictive biomarkers of tasquinimod efficacy may be warranted to determine whether certain subgroups will derive an OS advantage. Data from the phase II trial suggested that men with low baseline thrombospondin-1 levels derived the greatest benefit from tasquinimod.[16] Because tasquinimod is

known to increase this antiangiogenic marker in preclinical tumor models,[28] there may be a mechanistic basis for further examination of predictive biomarkers identified in this study. Preclinical evidence also suggests that tasquinimod has immunomodulatory activity, shown as an inhibitory effect on myeloid-derived suppressive cells and M2-polarized tumor-associated macrophages.[13] Identification of a potential immunologic biomarker will help with patient selection and determination of the most rational combination strategy for developing S100A9 inhibitors.

The tolerability of tasquinimod was good overall, and the vast majority of patients were able to escalate to the maximum 1-mg/day dose according to the predefined schedule. Dose interruptions or reductions were infrequent, and the overall safety profile was consistent with that observed in the phase II study. Tasquinimod was associated with a higher rate of withdrawals as a result of AEs. GI and musculoskeletal disorders occurred at a slightly higher frequency with tasquinimod, as seen in the phase II study. The overall incidence of cardiovascular events was low but, as observed previously,[15,16] was slightly higher with tasquinimod. This higher rate of cardiovascular events may have contributed to the lack of survival benefit due to early drug discontinuation. However, treatment-related deaths were not increased with tasquinimod, suggesting lack of efficacy rather than toxicity as the main contributing factor.

In conclusion, this phase III study confirmed that tasquinimod improved rPFS in patients with mCRPC compared with placebo. This benefit did not translate into an improvement in OS. The tolerability profile of tasquinimod was consistent with that in previous studies. On the basis of the lack of OS benefit observed in this study, further clinical development of tasquinimod in this patient population was not pursued.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized, Double-Blind, Placebo-Controlled Phase III Study of Tasquinimod in Men With Metastatic Castration-Resistant Prostate Cancer

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 jco.ascopubs.org/site/ifc.

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Acknowledgment

We thank Neil Anderson from Adelphi Communications who provided medical writing support that was funded by Ipsen.

Appendix

Table A1. Phase III Study Sites (241) in 37 Countries

Site	Principal Investigator
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Royal Prince Alfred Hospital, Camperdown	Lisa Horvath, MBBS, PhD
India	
Jehangir Clinical Development Centre, Pune	Bhalchandra Kashyapi, MBBS, MCh, MS
New Zealand	
Tauranga Urology Research, Tauranga	Peter Gilling, MD
Canterbury Urology Research Trust, Christchurch	Frank Kueppers, MD, PhD
Roundhay Medical Centre and Nelson Public Hospital, Nelson; Wairau Public Hospital, Blenheim	Patrick Meffan, MBChB, FRACS
Palmerston North Hospital, Palmerston North	Quinten King, MBBCh, FRCS
Korea	
Gangnam Severance Hospital, Seoul	Byung Ha Chung, MD, PhD
Chonnam National University Hospital, Gwangju	Taek Won Kang, MD, PhD
Seoul St Mary's Hospital, Seoul	Sae Woong Kim, MD, PhD
Asan Medical Center, Seoul	Choung-Soo Kim, MD
Severance Hospital, Seoul	Sung Joon Hong, MD, PhD, MS
Samsung Medical Center, Seoul	Hyun Moo Lee, MD, PhD
Taiwan	
Chang Gung Medical Foundation, Taoyuan	Cheng-Keng Chuang, MD
Taichung Veterans General Hospital, Taichung	Yen-Chuan Ou, MD, PhD
National Taiwan University Hospital, Taipei	Yu-Chieh Tsai, MD
Kaohsiung Veterans General Hospital, Kaohsiung	Tong-Lin Wu, MD, EMBA
China	
Urology Surgery Department, Beijing	Lijun Chen, MD
Fudan University Shanghai Cancer Center, Shanghai	Dingwei Ye, MD
Chengdu Military General Hospital, Chengdu	Liang Wang, MD
Urology Surgery Department, Shantou	Junhong Zheng, MD
Huashan Hospital, Shanghai	Qiang Ding, MD
Zhongnan Hospital of Wuhan University, Wuhan	Fuxiang Zhou, MD
Argentina	
Centro Oncológico "Ágave," Santa Fe	Natalia Broglia Sicco, MD
Centro de Diagnóstico Urológico, Buenos Aires	Luis Fernando Montes de Oca, MD
Centro Oncológico Fundacion Koria, St Rosa	Pablo Picon, MD
Hospital Italiano de Buenos Aires, Buenos Aires	María Pallotta, MD
Brazil	
Hospital Evangelico de Cachoeiro de Itapemirim, Cachoeiro de Itapemirim	Sabina Aleixo, MD
Granbery Juiz de Fora Hospital Universitario da Universidade Federal de Juiz de Fora Avenue Eugenio do Nascimento, Juiz de Fora	Christiane Alves, MD
Rio de Janeiro Hospital St Maria Madalena Estrada do Dende, Rio de Janeiro	Iane Cardoso, MD
Natal Liga Norte Riograndense Contra o Cancer Unidade I Hospital Luiz Antonio, Natal	Danielli Matias, MD
Florianopolis Hospital, Bala Sul Medical Center, Florianopolis	Yeni Neron, MD
Salvador Hospital da Bahia, Salvador	José Nogueira, MD
Sao Paulo Centro de Pesquisa Clinical, Sao Paulo	Roberto Rocha, MD
Centro Oncologico Mogi das Cruzez, Sao Paulo	Daniel Grabarz, MD
Passo Fundo Hospital Sao Vicente de Paulo, Passo Fundo	Luis Schlittler, MD
Hospital de Clinicas de Porto Alegre, Porto Alegre	Gilberto Schwartsmann, MD
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(continued on following page)

Table A1. Phase III Study Sites (241) in 37 Countries (continued)

Site	Principal Investigator
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Erasme Hospital, Université Libre de Bruxelles, Brussels	Thierry Roumeguère, MD
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Oncology Center Plovdiv, Plovdiv	Petar Petrov, MD
Hospital Oncology Disease Medical Oncotherapy and Palliative Care Base II, Varna	Violina Taskova, MD
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France	
Central Hospital Cannes, Cannes	Regis Kaphan, MD
Beau Soleil Clinic, Montpellier	Xavier Rebillard, MD
Foch Hospital, Suresnes	Christine Theodore, MD
Regional Center de Lutte, Angers	Rémy Delva, MD
Centre Hospital Lyon-Sud, Pierre-Benite	Alain Ruffion, MD
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(continued on following page)

Table A1. Phase III Study Sites (241) in 37 Countries (continued)

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Regional Osrodek Oncology, Lodz	Ewa Kalinka-Warzocha, MD
EuroMediCare, Wroclaw	Rafal Kmieciak, MD
Wojewodki Hospital Urology Clinic, Bialystok	Robert Kozlowski, MD, PhD
Wielkopoiskie Oncology Center, Poznan	Piotr Milecki, MD, PhD
LexMedica Rudolfa, Wroclaw	Zenona Jablonska, MD
Romania	
Oncolab, Craiova	Dan Lungulescu, MD
Fundeni Clinical Institute, Bucharest	Mihai Harza, MD
Sf loan cel Nou Emergency County Hospital, Suceava	Doina Ganea, MD, PhD
The Oncology Institute, Cluj Napoca	Cristina Cebotaru, MD; Tudor Ciuleanu, MD, PhD
Opris Emergency County Hospital, Baia Mare	Dumitru Filip, MD
Oncomed SRL, Timisoara	Cristina Oprean, MD
Ianuli Medical Consult SRL, Bucharest	Carmen Ianuli, MD
Municipal Hospital Ploiesti, Ploiesti	Gabriel Doru Ghizdavescu, MD

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Table A1. Phase III Study Sites (241) in 37 Countries (continued)

Site	Principal Investigator
Russia	
Omsk Healthcare, Oncology Center, Omsk	Evgeniy Kopyltsov, MD, PhD
Clinic Andros Lenina Street, St Petersburg	Alexey Plekhanov, MD, PhD
Leningrad Regional Oncology Center, St Petersburg	Denis Khvorostenko, MD
St Petersburg Healthcare City Hospital, St Petersburg	Vakhtang Shanava, MD, PhD
Vladimir Healthcare Oncology Center, Vladimir	Natalya Rodicheva, MD
Orkli, Sredniy Prospekt, St Petersburg	Vladimir Kheifets, MD, PhD
Federal State Institution Moscow Research Oncology Institute, Moscow	Boris Alekseev, MD, PhD
State Institution of Healthcare Sverdlovsk Regional Hospital, Ekaterinburg	Alexander Zyryanov, MD
Regional State Institution of Healthcare Novosibirsk Regional Oncology Centre, Novosibirsk	Marat Zaripov, MD
Slovak Republic	
Ambulatory Urology Clinic, Trecin	Roman Sokol, MD
Cuimed, Bratislava	Frederico Goncalves, MD, PhD
Spain	
Hospital Clinic 1 Provincial Oncology Servico de Oncologia Medica, Barcelona	Begoña Mellado, MD
Corporacio Sanitaria Parc Tauli Hospital de Sabadell Servicio de Oncologia Medica, Barcelona	Enrique Gallardo, MD
Hospital Infanta Sofia, Madrid	Emilio Ríos, MD
Clinica Universidad de Navarra Servicio de Oncologia, Pamplona	Jose Luis Perez Gracia, MD
Hospital Universitario Virgen del Rocio Servicio de Oncologia Medica Ave Manuel Siurot, Sevilla	Begoña Pérez Valderrama, MD
Hospital Clinico Universitario de Valencia Servicio de Oncologia Medica, Valencia	Isabel Chirivella, MD
Hospital Universitario Marques de Valdecilla Servicio de Oncologia Medica, Santander	Marta Lopez-Brea Piqueras, MD
Hospital Universitario Vall D'Hebron Servicio de Oncologia-Unidad, Barcelona	Joan Carles Galceran, MD
Hospital de la Santa Creu, Barcelona	José Pablo Maroto, MD
Hospital Universitario Fundacion Alcorcon Servicio de Oncologia Medica, Alcorcon	Susana Hernando Polo Jesus, MD; Garcia-Donas Jimenez, MD
Hospital Clinico Universitario "Lozano Blesa" Servicio de Oncologia Medica, Zaragoza	Alberto Saenz Cusi, MD
Hospital Universitario Central de Asturias Servicio de Oncologia, Oviedo	Emilio Esteban Gonzalez, MD; Enrique Estrada, MD
Instituto Valenciano de Oncologia, Valencia	Eduardo Solsona Narbon, MD
Sweden	
Radiumhemmet Karolinska University Hospital, Stockholm	Sten Nilsson, MD
Sahlgrenska University Hospital, Gothenburg	Jan-Erik Damber, MD
Central Hospital Karlstad Oncology Clinic, Karlstad	Claes Ginman, MD
Turkey	
Istanbul University Cerrahpasa School of Medicine, Istanbul	Can Obek, MD
Ukraine	
Municipal Institution of Healthcare VI Shapoval Regional Clinical Centre of Urology and Nephrology Urology Department #4, Kharkiv	Igor Antonyan, MD, PhD
Ivano-Frankivsk Regional Oncology, Dispensary Clinical Mammology Centre, Department with Urology Beds Ivano-Frankivsk	Volodymyr Romanchuk, MD; Ipolit Kostinskyy, Professor, MD, PhD
Municipal Institution, Multifield City Clinical Hospital #4, Department of Chemotherapy, Dnipropetrovsk	Igor Bondarenko, Professor, MD, PhD
Municipal Institution, Zaporizhzhia Regional Clinical Hospital of Zaporizhzhia Regional Council, Urology Department; State Institution Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine Chair of Urology, Zaporizhzhya	Olexiy Lyulko, Professor, MD
Kyiv City Clinical Hospital #3 Urology Department, Kyiv	Petro Ivashchenko, MD
Municipal Institution, Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov, Urology Department #2, Dnipropetrovsk State Medical Academy Chair of Urology, Operative Surgery and Topographic Anatomy, Dnipropetrovsk	Olexiy Lyulko, Professor, MD; Viktor Stus, Professor, MD
Regional Municipal Institution, Chernivtsi Regional Clinical Hospital, Chemivtsi	Valerii Zaitsev, Professor, MD
Kyiv Oleksandrivska Clinical Hospital, Urology Department #3, Kyiv	Sergii Pasiechnikov, Professor, MD
Uzhgorod Central City Clinical Hospital, City Oncology Centre, Uzhgorod	Yevhen Hotko, MSD, MD, PhD
Municipal Clinical Medical and Preventive Treatment Institution, Donetsk Regional Antitumour Centre, Donetsk	Andriy Anishchenko, MD
Medical and Preventive Treatment Institution, Volyn Regional Oncology Dispensary, Lutsk	Orest Andrusenko, MD
Lviv State Oncology Regional Treatment and Diagnostic Center, Lviv	Yaroslav Shparyk, MD, PhD
Municipal Treatment-Prophylactic, Institution Central City Clinical Hospital, Donetsk	Yuri Semyak, MD

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Table A1. Phase III Study Sites (241) in 37 Countries (continued)

Site	Principal Investigator
Municipal Institution of Kyiv Regional Council, Kyiv Regional Oncology Dispensary, Kyiv	Iurii Golovko, MD
Center of Reconstructive and Restorative Medicine (University Clinic) of Odesa National Medical University, Odesa	Nataliia Tavartkiladze, MD
United Kingdom	
St James University Hospital, Leeds	William Cross, MD
Royal Marsden Hospital, Sutton	Robert Huddart, MD
Mount Vernon Hospital, Northwood	Peter Hoskin, MD
Oxford Cancer Centre, Headington	Andrew Protheroe, MD
St Richard's Hospital, Chichester	James Hicks, MD; Paul Carter, MD
Scunthorpe General Hospital, Scunthorpe	Sanjay Dixit, MD
Sarah Cannon Research, London	Simon Chowdhury, MA, MBBS, MRCP, PhD
University Hospitals Birmingham National Health Service Foundation Trust Queen Elizabeth Hospital, Birmingham	Nicholas James, MD
Nottingham University Hospitals National Health Service Trust, Nottingham	Santhanam Sundar, MD
Canada	
The Fe/Male Health Centre, Oakville, ON	Richard Casey, MD
Probity Medical Research, North York, ON	Stanley Flax, MB, BCh
Southern Interior Medical Research, Kelowna, BC	Thomas Kinahan, MD
Mor Urology, Newmarket, ON	Morrie Liquornik, MD
Pacific Urologic Research, Victoria, BC	Gary Steinhoff, MD
St Joseph's Lifecare Centre, Brantford, ON	Wilson Leung, MD
United States	
Duke University Medical Center, Durham, NC	Andrew Armstrong, MD
Peachtree Hematology-Oncology Consultants, Atlanta, GA	Vasileios John Assikis, MD
Urologic Consultants of Pennsylvania, Bala Cynwyd, PA	Laurence H. Belkoff, DO
Pacific Urology Institute, Santa Monica, CA	Stanley Brosman, MD
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD	Michael Carducci, MD
Ventura County Hematology Oncology Specialists, Oxnard, CA	Kevin Q. Chang, MD
Vanderbilt University Medical Center, Nashville, TN	Sam Chang, MD
Clinical Trials Office, Dallas, TX	James Cochran, MD
University of Pittsburgh Physicians Department of Urology, Pittsburgh, PA	Jeffrey Gingrich, MD
Premier Medical Group, Poughkeepsie, NY	Evan R. Goldfischer, MD
Midwest Urology Associates, Melrose Park, IL	Richard G. Harris, MD
Lawrenceville Urology, Lawrenceville, NJ	Gary S. Karlin, MD
Capitol Comprehensive Cancer Care Clinic, Jefferson City, MO	Ali Khojasteh, MD
Carolina Urology Partners, Concord, NC	David U. Lipsitz, MD, FACS, CPI
Palm Beach Urology Associates, Wellington, FL	Georgis Patsias, MD
Roswell Park Cancer Center Institute, Buffalo, NY	Roberto Pili, MD
Grand Strand Urology, Myrtle Beach, SC	Neal Shore, MD, FACS
Lancaster Urology, Lancaster, PA	Paul R. Sieber, MD
Boise Urology, Meridian, ID	Joseph H. Williams, MD
Metropolitan Urology, Jeffersonville, IN	James L. Bailen, MD
Frankel, Reed & Evans, Burien, WA	Jeffrey M. Frankel, MD
Virginia Oncology Associates, Norfolk, VA	Mark T. Fleming, MD
Virginia Cancer Specialists, Fairfax, VA	Alexander I. Spira, MD
Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX	Thomas E. Hutson, DO
Blue Ridge Cancer Care, Roanoke, VA	Mark D. Kochenderfer, MD
Willamette Valley Cancer Institute and Research Center, Eugene, OR	Joseph A. Fiorillo, MD; John R. Caton Jr, MD
Comprehensive Cancer Centers of Nevada, Las Vegas, NV	Nicholas J. Vogelzang, MD
Raleigh Hematology Oncology Associates, DBA Cancer Centers of North Carolina, Raleigh, NC	William R. Berry, MD
University of Utah/Huntsman Cancer Center, Salt Lake City, UT	Neeraj Agarwal, MD
Associates in Oncology/Hematology, Rockville, MD	Manish Agrawal, MD
Oncology Specialists, Park Ridge, IL	Timothy Lestingi, MD; Chadi Nabhan, MD
John Theurer Cancer Center at Hackensack, Hackensack, NJ	Robert Alter, MD
Redwood Regional Medical Group, Santa Rosa, CA	Wes S. Lee, MD
Arizona Oncology Associates, Tucson, AZ	Christopher Di Simone, MD
Tufts Medical Center, Boston, MA	Paul Mathew, MD

Table A2. Other Secondary Efficacy End Points

Outcomes	Tasquinimod (n = 832)		Placebo (n = 413)				
	Median (months)	95% CI	Median (months)	95% CI	HR	95% CI	*P*
New bone lesion							
Local	8.3	6.0 to 9.5	4.5	3.1 to 5.6	0.723	0.616 to 0.848	< .001
Central	8.1	6.0 to 8.5	4.8	3.1 to 5.6	0.735	0.623 to 0.867	< .001
New soft tissue lesion							
Local	19.4	16.6 to 25.3	11.1	8.6 to 16.4	0.612	0.493 to 0.760	< .001
Central	20.5	19.3 to NR	19.1	11.5 to NR	0.678	0.531 to 0.866	.002
First radiologic or symptomatic progression							
Local	4.8	4.1 to 5.5	3.2	2.9 to 4.2	0.812	0.714 to 0.925	.002
Central	5.2	4.4 to 5.6	3.7	3.1 to 4.4	0.849	0.745 to 0.967	.013
First radiologic or symptomatic progression or death							
Local	4.8	4.0 to 5.5	3.2	2.9 to 4.1	0.812	.716 to .922	.001
Central	5.2	4.4 to 5.6	3.6	3.1 to 4.3	0.845	0.744 to 0.959	.009
Tumor-related pain progression*	5.6	4.9 to 6.0	8.3	6.7 to 10.8	1.259	1.097 to 1.445	< .001
KPS deterioration	11.7	10.3 to 13.6	17.4	14.5 to 19.1	1.292	1.110 to 1.505	< .001
PSA doubling time	5.2	4.5 to 5.6	3.3	2.9 to 4.0	0.734	0.631 to 0.853	< .001

Abbreviations: HR, hazard ratio; KPS, Karnofsky performance status; NR, not reached; PSA, prostate-specific antigen.
*Including palliative interventions.