

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

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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 \geq 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 \geq 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.

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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 $\geq 70\%$. 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 ($\geq 90\%$ 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 boundaries²⁰: 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% ν 14.5%). Median time since diagnosis was shorter in the tasquinimod group than in the placebo group (45.7 ν 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 ν placebo) were radiographic progression (23.8% ν 36.5%), symptomatic progression requiring new anti-cancer therapy (21.3% ν 18.8%), and poor tolerability or AEs (17.9% ν 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) 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 ν 8.1 months; $P = .001$), as was time to initiation of further cytotoxic therapy (25.8 ν 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 ν seven patients [1.7%] in the placebo group) or enzalutamide (zero ν one [0.2%]). These treatments were more commonly

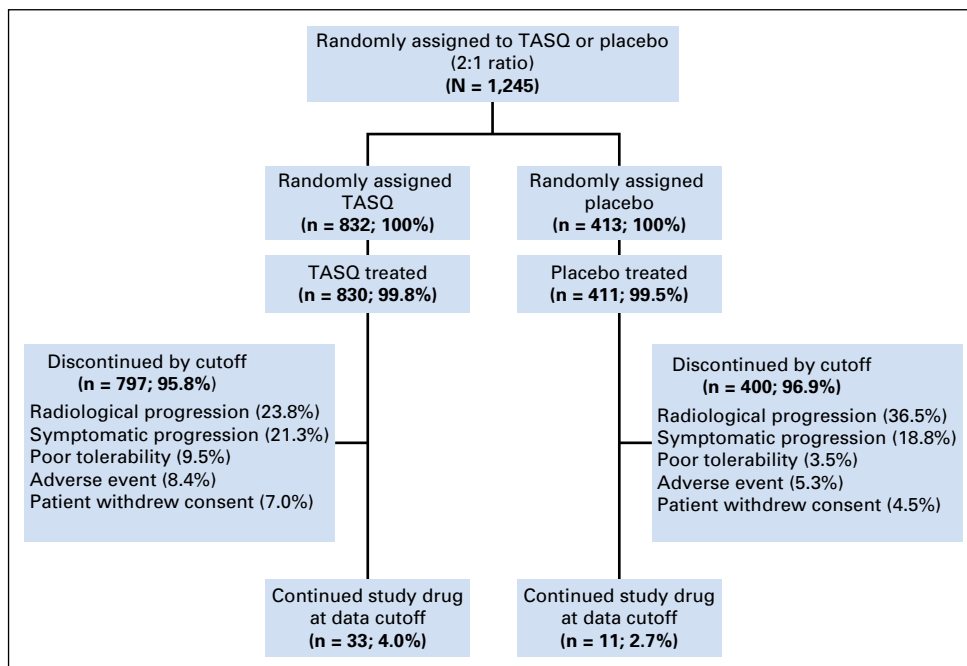


Fig 1. CONSORT diagram. TASQ, tasquinimod.

| Table 1. Baseline Demographic and Disease Characteristics | | | | |
|---|--------------------------|------|----------------------|------|
| Characteristic | Tasquinimod (n = 832) | | Placebo (n = 413) | |
| | No. | % | 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.

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%]).

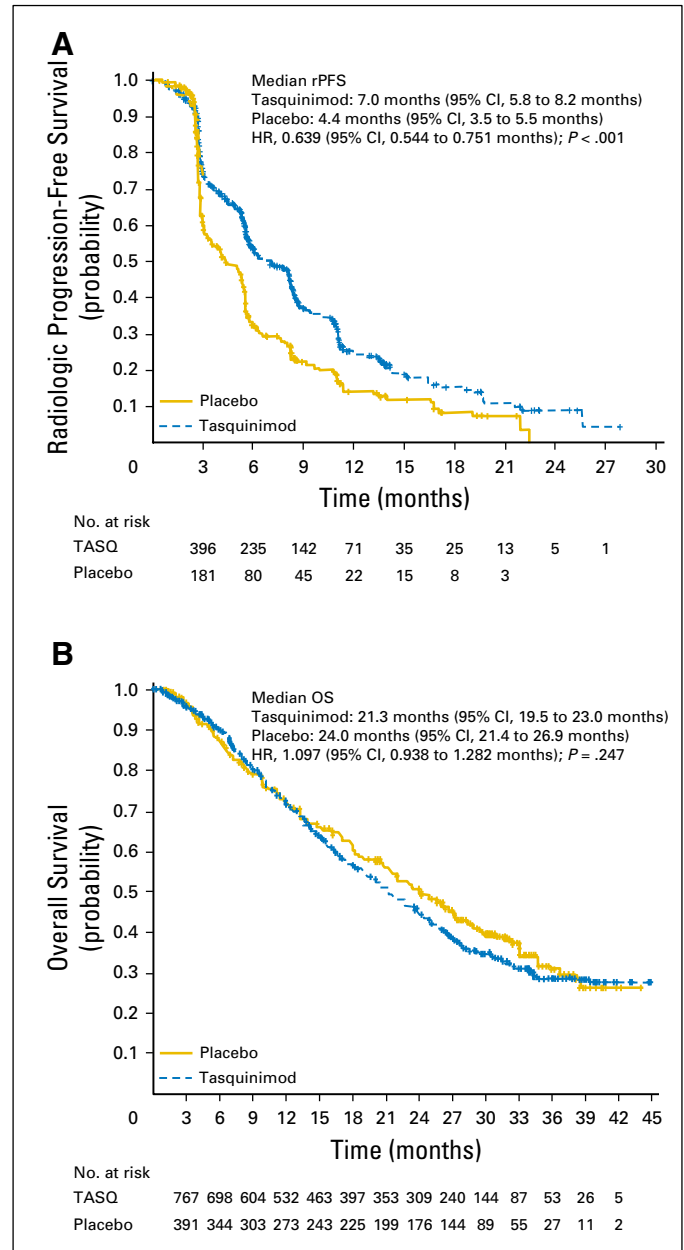


Fig 2. Kaplan-Meier analysis of (A) radiologic progression-free survival (rPFS; central review) and (B) overall survival (OS). HR, hazard ratio; TASQ, tasquinimod.

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.

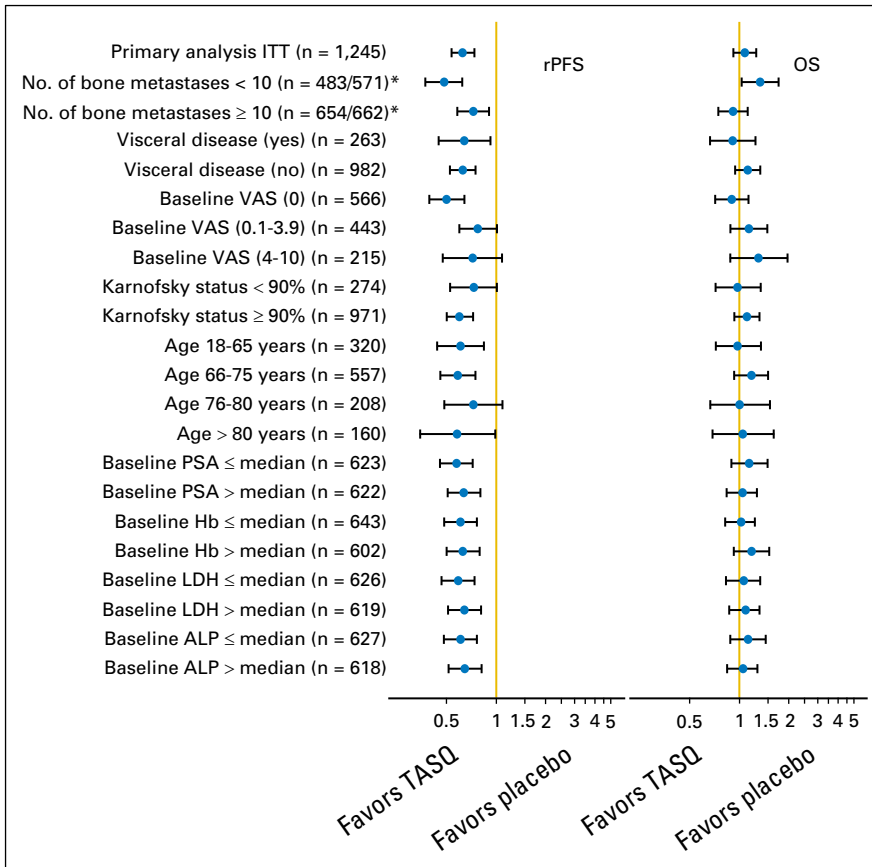


Fig 3. Radiologic progression-free survival (rPFS) and overall survival (OS) outcomes in patient subgroups. *Number of patients included in analyses of rPFS/OS. ALP, alkaline phosphatase; Hb, hemoglobin; ITT, intent to treat; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; TASQ, tasquinimod;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

| Progression | Tasquinimod (n = 832) | | Placebo (n = 413) | | HR | 95% CI | P |
|---|-----------------------|--------------|-------------------|--------------|-------|----------------|--------|
| | Median (months) | 95% CI | Median (months) | 95% CI | | | |
| 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

| AE | Tasquinimod (n = 830) | | | | Placebo (n = 411) | | | |
|--------------------|--------------------------|------|------------------|------|----------------------|------|------------------|------|
| | All Grades | | Grades 3 to 5 | | All Grades | | Grades 3 to 5 | |
| | 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 progression⁷ 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 mCRPC²⁴⁻²⁶ 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

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Travel, Accommodations, Expenses: Pfizer, Novartis, Astellas Pharma, Janssen Oncology, Pierre Fabre, Sanofi

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Appendix

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

| Site | Principal Investigator |
|---|---|
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| Coffs Harbor Health Campus, Coffs Harbor | Karen Briscoe, MBBS |
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| 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 Broglio Sicco, MD |
| Centro de Diagnóstico Urológico, Buenos Aires | Luis Fernando Montes de Oca, MD |
| Centro Oncológico Fundacion Korla, 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 Clinica, Sao Paulo | Roberto Rocha, MD |
| Centro Oncologico Mogi das Cruzes, Sao Paulo | Daniel Grabarz, MD |
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Table A1. Phase III Study Sites (241) in 37 Countries (continued)

| Site | Principal Investigator |
|--|--|
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| Clinicia Alemana de Temuco, Temuco | Mario Gorena, MD |
| Uromed Ave Salvador 351, Santiago | Anibal Salazar Huerta, MD |
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| Fundacion Clinica Valle del Lili, Cali | Manuel Duque Galan, MD |
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| Mexico | |
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| Hospital Aranda de la Parra, Guanajuato | Marco Badillo Santoyo, MD |
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| Panama | |
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| Algemeen Ziekenhuis Maria Middelaes, Gent | Filip Ameye, MD |
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| Oncology Center Plovdiv, Plovdiv | Petar Petrov, MD |
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| France | |
| Central Hospital Cannes, Cannes | Regis Kaphan, MD |
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| Regional Center de Lutte, Angers | Rémy Delva, MD |
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Tasquinimod in Metastatic Castration-Resistant Prostate Cancer

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

| Site | Principal Investigator |
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| Greece Alexandra Hospital Department of Clinical Therapeutics, Athens Athens Oncology Hospital Urology Clinic, Athens Thessaloniki General Hospital, Thessaloniki Patras University General Hospital, Rion Patras | Eleni Efstathiou, MD, PhD Anastasios Thanos, MD Athanasios Papatthanasious, MD Petros Perimenis, MD |
| Israel Oncology Institute, The Chaim Sheba Medical Center, Tel Hashomer The Lady Davis Carmel Medical Center, Haifa Assaf Harofe Medical Center Oncology Department, Zerifin Tel Aviv Sourasky Medical Center, Oncology Department, Tel Aviv Oncology Institute Rambam Health Care Campus, Haifa Institute of Oncology Davidoff Cancer Center, Rabin Medical Center, Tikva Bnai Zion Medical Center, Haifa Sharett Institute of Oncology, Hadassah University Hospital, Jerusalem Soroka University Medical Center, Be'er Sheva | Raanan Berger, MD, PhD Avi Stein, MD Avishay Sella, MD Eliahu Gez, MD Avivit Peer, MD Eli Rosenbaum, MD Ofer Nativ, MD Stephen Frank, MD Wilmosh Mermershtain, MD |
| Italy San Camillo Forlanini Hospital, Rome Scientific Institute Romagnolo Via Piero Maroncelli, Meldola Oncology Institute Veneto, Padova Hospital di Lecco, Lecco Oncologia Falck Hospital, Niguarda Ca Granda Piazzale Hospital, Milan Azienda Ospedaliero Universitaria Giovanni Battista di Torino Molinette, Turin Istitute di Cremona, Cremona Ospedale degli Infermi di Faenza Unità di Oncologia di Oncologia Medica, Faenza Hospital San Carlo Borromeo, Milan | Cora Sternberg, MD Cecilia Menna, MD Umberto Basso, MD Antonio Ardizzoia, MD Salvatore Siena, MD Libero Ciuffreda, MD Rodolfo Passalacqua, MD Francesco Carrozza, MD; Giorgio Cruciani, MD Maria Locatelli, MD |
| Latvia Riga Eastern Clinical University Hospital, Latvian Oncology Center, Riga Private practice of Dzintra Litavniece, Liepaja P. Stradins Clinical University Hospital, Riga | Arija Brize, MD Dzintra Litavniece, MD Egils Vjaters, MD |
| Lebanon Middle East Institute of Health, Bsalim El Meten American University of Beirut Medical Center, Beirut | Abi Gerges Dany, MD Ali Shamseddine, MD |
| Lithuania Vilnius University Hospital, Vilnius Institute of Oncology Vilnius University, Vilnius Lithuanian University Health Sciences Kaunas Clinics, Kaunas | Feliksas Jankevicius, MD Albertas Ulys, MD, PhD Daimantas Milonas, MD |
| The Netherlands St Elizabeth Hospital, Tilburg Martini Ziekenhuis, Groningen Canisius Wilhelmina Hospital, Nijmegen Leiden University Medical Center, Leiden Vrije Universiteit Medical Center, Amsterdam University Medical Center St Radboud, Nijmegen | P. Kil, MD, PhD L.F.A. Wymenga, MD, PhD H. Vergunst, MD A.J. Gelderblom, MD R.J.A. van Moorselaar, MD P.F.A. Mulders, MD |
| Poland Curie Oncology Institute, Nowotworow Oncology Clinic, Warsaw Niepubliczny Zaklad Opieki Zdrowotnej Urology Center, Myslowice Regional Osrodek Oncology, Lodz EuroMediCare, Wroclaw Wojewodki Hospital Urology Clinic, Bialystok Wielkopolskie Oncology Center, Poznan LexMedica Rudolfa, Wroclaw | Tomasz Demkow, MD, PhD Adam Dobrowolski, MD Ewa Kalinka-Warzocho, MD Rafal Kmieciak, MD Robert Kozlowski, MD, PhD Piotr Milecki, MD, PhD Zenona Jablonska, MD |
| Romania Oncolab, Craiova Fundeni Clinical Institute, Bucharest Sf Ioan cel Nou Emergency County Hospital, Suceava The Oncology Institute, Cluj Napoca Opris Emergency County Hospital, Baia Mare Oncomed SRL, Timisoara Ianuli Medical Consult SRL, Bucharest Municipal Hospital Ploiesti, Ploiesti | Dan Lungulescu, MD Mihai Harza, MD Doina Ganea, MD, PhD Cristina Cebotaru, MD; Tudor Ciuleanu, MD, PhD Dumitru Filip, MD Cristina Oprean, MD Carmen Ianuli, MD 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 Servicio 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 Kostinsky, 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, Zaporizhzhia | 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, Chernivtsi | Valerii Zaitsev, Professor, MD |
| Kyiv Oleksandrivska Clinical Hospital, Urology Department #3, Kyiv | Sergii Pasichnikov, 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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Tasquinimod in Metastatic Castration-Resistant Prostate Cancer

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 | Natalia 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 |
| Probit 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) | | HR | 95% CI | P |
|--|--------------------------|--------------|----------------------|--------------|-------|----------------|--------|
| | Median (months) | 95% CI | Median (months) | 95% CI | | | |
| 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.