Report from the FDA

Approval Summary: Docetaxel in Combination with Prednisone for the Treatment of Androgen-Independent Hormone-Refractory Prostate Cancer

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ABSTRACT

Purpose: **Docetaxel, a taxane previously approved for the treatment of breast cancer and non–small cell lung cancer, was approved by the United States Food and Drug Administration on May 19, 2004 for use in combination with prednisone for the treatment of metastatic androgen-independent (hormone-refractory) prostate cancer. The purpose of this summary is to review the database supporting this approval.**

Experimental Design: **In a randomized, global study enrolling 1,006 patients, two schedules of docetaxel were compared with mitoxantrone + prednisone as follows: MTZ q 3w, mitoxantrone 12 mg/m2 every 21 days + prednisone 5 mg twice a day for a total of 10 cycles; TXT q 3w, docetaxel 75 mg/m^2 every 21 days + prednisone 5 mg twice a day for a total of 10 cycles; and TXT qw, docetaxel 30 mg/m^2 days 1, 8, 15, 22, and 29 every 6 weeks + prednisone 5 mg twice a day for a total of 5 cycles.**

Results: **There was a statistically significant overall survival advantage shown for the TXT q 3w arm over MTZ q 3w (median survival 18.9 months *versus* 16.5 months, $P = 0.0094$). No overall survival advantage was shown for TXT qw compared with MTZ q 3w. The most commonly occurring adverse events included anemia, neutropenia, infection, nausea, sensory neuropathy, fluid retention, alopecia, nail changes, diarrhea, and fatigue.**

Conclusions: **This report describes the Food and Drug Administration review supporting this first approval of a combination therapy for hormone-refractory prostate cancer based on demonstration of a survival benefit.**

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INTRODUCTION

Docetaxel (Taxotere, Aventis Pharmaceuticals, Bridgewater, NJ) is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules. Microtubules bundles without normal function are produced, and mitosis is inhibited. Docetaxel has been previously approved by the United States Food and Drug Administration (FDA) for locally advanced or metastatic breast cancer after anthracycline therapy, locally advanced or metastatic non–small-cell lung cancer after prior platinum-based chemotherapy, and for use in combination with cisplatin for newly diagnosed locally advanced or metastatic non–small cell lung cancer.

After development of metastatic hormone-refractory disease, prostate cancer is incurable, with median survival of 9 to 12 months (1, 2). Historically, no single agent or combination regimen has shown a survival benefit in this setting. In 1996, mitoxantrone administered in combination with prednisone was approved by the FDA for the palliative treatment of metastatic or locally advanced disease that had progressed on standard hormonal therapy. This approval was based on results of a randomized trial comparing mitoxantrone plus prednisone to prednisone alone. A total of 161 patients were randomized in this trial, which used palliative response as a primary endpoint (3, 4). A second randomized trial of mitoxantrone plus hydrocortisone *versus* hydrocortisone alone conducted by the Cancer and Leukemia Group B provided supportive evidence of a palliative effect (4).

Docetaxel has been evaluated in single arm studies in hormone-refractory prostate cancer, either as a single dose every 3 weeks or a weekly regimen. Prostate-specific antigen (PSA) declines, and radiographic responses in those patients with bidimensionally measurable lesions were noted (5–9).

TAX327, a global multicenter trial, was designed to evaluate two docetaxel schedules with prednisone compared with a control arm of mitoxantrone plus prednisone. The design and findings of this study are outlined below.

TREATMENT PLAN

Patients were randomized to one of three treatments as follows:

The treatment plan is also outlined in Fig. 1.

MTZ q 3w. Mitoxantrone 12 mg/m^2 intravenously (day 1) as a 30-minute infusion every 21 days plus prednisone 5 mg orally twice daily for 10 cycles. Prednisone could be continued after completion of 10 cycles.

TXT q 3w. Docetaxel 75 mg/m^2 intravenously (day 1) as a 1-hour infusion every 21 days plus prednisone 5 mg orally

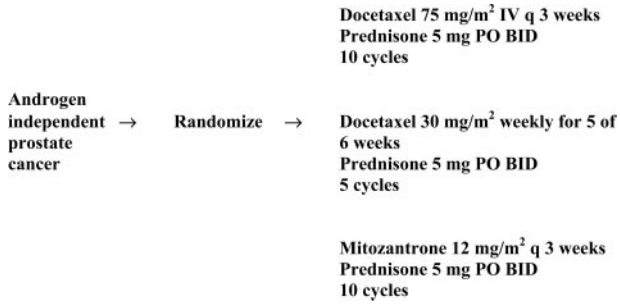

Fig. 1 Treatment schema.

twice daily for 10 cycles. Prednisone could be continued after completion of 10 cycles. Prophylactic dexamethasone 8 mg was to be administered orally at 12 hours, 3 hours and 1 hour before docetaxel.

TXT qw. Docetaxel 30 mg/m^2 intravenously as a 30-minute infusion on days 1, 8, 15, 22, and 29 every 6 weeks plus prednisone 5 mg orally twice daily for 5 cycles. Prednisone could be continued after completion of 5 cycles. Dexamethasone 8 mg was to be administered orally 1 hour before docetaxel infusion.

PATIENT POPULATION/DEMOGRAPHICS

The main protocol-specified inclusion criteria included histologically or cytologically proven adenocarcinoma of the prostate, metastatic disease unresponsive or refractory to hormone therapy (castration by orchiectomy and/or androgen blockade), and Karnofsky Performance Status ≥60. Except for estramustine monotherapy, prior chemotherapy was not allowed. Treatment with bisphosphonates had to be discontinued before randomization. Patients with symptomatic peripheral neuropathy grade ≥2 (National Cancer Institute Common Toxicity Criteria version 2.0), known brain or leptomeningeal involvement, or prior radiotherapy to >25% of bone marrow were excluded.

Age, race, Karnofsky performance status at baseline, staging, baseline PSA, and Gleason score are listed by distribution across the three study arms in Table 1. These seem to be evenly distributed across treatment groups. Approximately 84 to 89% of patients enrolled to each treatment arm had a baseline PSA ≥20. All of the patients had received prior hormonal therapy and/or surgery for hormonal control. Approximately half of all of the patients in each treatment had received prior radiation therapy, and ~20% of the patients had received prior estramustine.

EFFICACY

The primary efficacy endpoint was survival, defined as time from randomization to the date of death from any cause. The primary analysis was done on the intent-to-treat population, consisting of all of the randomized patients. The study cutoff date for the primary analysis was March 24, 2003, the date on which the sponsor received notification of the 535th event. By that date, a total of 557 events had occurred. All of the subjects known to be alive at the cutoff date were censored either on the date of last assessment or on the cutoff date if the last contact had taken place subsequently.

Three simultaneous comparisons of overall survival were done with a modified Bonferroni adjustment to control for multiplicity (10); TXT q 3w *versus* control MTZ q 3w, TXT q w *versus* control MTZ q 3w, or the two pooled docetaxel treatment groups *versus* the control. The proposed nominal significance level for each comparison to MTZ q3w is as follows: Combined TXT groups, 0.04; TXT q 3w, 0.0175; and TXT q w, 0.0175. The primary analysis was to be considered positive if at least one of the three adjusted log-rank test comparisons was less than the prespecified nominal significance level for that comparison.

The stratified log-rank test (stratified on baseline pain and Karnofsky performance status) was prospectively specified as the primary means of determining if TXT q 3w and/or TXT q w increased overall survival compared with MTZ q 3w.

Overall survival was significantly superior in the TXT q3w group compared with the MTZ q 3w group (median survival 18.9 months *versus* 16.50 months, $P = 0.0094$). Overall survival was also significantly superior for the combined TXT groups compared with the MTZ q 3w group. Overall survival for the once weekly docetaxel arm was not statistically significantly different from that of the MTZ q 3w group. Results of the comparison of TXT q 3w to MTZ q 3w are summarized in Table 2, and the Kaplan-Meier survival curve for this comparison is depicted in Fig. 2.

Secondary endpoints included pain response rate and du-

Table 1 Baseline patient characteristics

Characteristic	TXT q3w $n = 335$ (%)	TXT qw $n = 334$ (%)	MTZ q3w $n = 337$ (%)
Age (years)			
Median	68.0	69.0	68.0
Range	42–92	36–92	43–86
Race			
Black	8 (2.4)	8 (2.4%)	10 (3%)
Caucasian	312 (93.1%)	312 (93.4%)	312 (92.6%)
Hispanic	8 (2.4%)	7 (2.1%)	9 (2.7%)
Oriental	3 (0.9%)	2 (0.6%)	3 (0.9%)
Other	4 (1.2%)	5 (1.5%)	3 (0.9%)
Karnofsky PS (%)			
≥80	293 (87.5)	292 (87.4)	290 (86.1)
≤70	42 (12.5)	41 (12.3)	47 (13.9)
Missing	0	1 (0.3)	0
Staging at diagnosis			
I	0	1 (0.3)	1 (0.3)
II	54 (16.1)	49 (14.7)	56 (16.6)
III	60 (17.9)	48 (14.4)	51 (15.1)
IV	192 (57.3)	193 (57.8)	183 (54.3)
Missing	29 (8.7)	43 (12.9)	46 (13.6)
Gleason score			
2–4	19 (5.7)	13 (3.9)	23 (6.8)
5–7	123 (36.7)	121 (36.2)	119 (35.3)
8–10	105 (31.3)	102 (30.5)	93 (27.6)
Missing	88 (26.3)	98 (29.3)	102 (30.3)
Baseline PSA (ng/ml)			
Mean	537	404	409
Median	114	108	123
Range	0.15–40740	0–16709	0.3–8022

Abbreviations: PS, performance status; PSA, prostate-specific antigen.

Table 2 Overall survival comparison of TXT q3w to MTZ q3w

	TXT q3w	MTZ q3w
Number of patients	335	337
Median survival (months)	18.9	16.5
95% Confidence interval	(17.0–21.2)	(14.4–18.6)
Hazard ratio	0.761	N/A
95% Confidence interval	(0.619–0.936)	
P *	0.0094	N/A

* Stratified log-rank test. Threshold for statistical significance = 0.0175 because of 3 arms.

ration, PSA response rate and duration, tumor response, time-to-pain progression, time-to-PSA progression, and time-to-tumor progression. The FDA considered these secondary endpoints as exploratory and not supportive of a marketing claim for the following reasons: (*a*) there was no prespecified plan for adjustment for multiplicity or ordering of secondary endpoints; (*b*) only a portion of patients enrolled were evaluable for any one of these secondary endpoints; and (*c*) large proportions of patients were censored in the analyses for time-to-progression and response duration.

SAFETY

Docetaxel dose intensity was slightly lower in the weekly docetaxel regimen (96% of planned relative dose intensity, range 62 to 115%) *versus* the every 3 week regimen (98% of planned relative dose intensity, range 51 to 107%). These small differences are not likely to explain the difference found in efficacy outcome between the two docetaxel regimens.

Although >90% of patients enrolled on TAX327 had at least one reported treatment emergent adverse event, serious adverse events were less commonly reported in individual patients. Individual serious or life-threatening adverse events included infection, anemia, neutropenia, neuropathy, nausea, vomiting, diarrhea, and cardiac left ventricular dysfunction. Clinically relevant all grade and grade 3/4 treatment emergent adverse event observed in the TXTq3w and MTZ arms are presented in Table 3. Although allergic reactions (all grade) did occur more commonly on the TXTq3w arm, grade 3 or 4 events were observed in <1% of patients.

Neutropenia was the most commonly observed grade 3/4 cytopenia, occurring in 32% of patients in the TXT q 3w arm and 22% in the MTZ arm. Peripheral edema and weight gain were the major signs of fluid retention; severe or life-threatening fluid retention events were uncommon, occurring in <1% of patients across the three treatment arms. All grade cardiac left ventricular dysfunction events occurred more frequently on the MTZ q 3w arm compared with TXT q 3w (22.1% *versus* 9.6%), consistent with known cardiotoxicity of mitoxantrone, and grade 3/4 events occurred in 1.2% of patients on MTZ q 3w and 0.3% on TXT q 3w.

The incidence of deaths within 30 days of last treatment infusion was equally distributed across treatments: 3.3% for TXT q 3w, 3.3% for TXT q w, and 2.7% for MTZ q 3w. Most were attributed to malignant disease or "other" causes. Of the deaths occurring within 30 days of last infusion, one on the TXT q 3w arm and two on MTZ q 3w were attributed to drug toxicity.

DRUG-DRUG INTERACTIONS

Because prednisone is a known inducer of CYP3A4 and 3A5 (11), the two enzymes involved in docetaxel metabolism, (12) the sponsor investigated any potential effect on docetaxel clearance by prednisone when both drugs were administered in combination. The pharmacokinetics of docetaxel were assessed in a subset of patients enrolled to TAX327. A total of 25 patients enrolled to TXT q 3w and 15 enrolled to TXT q w had blood samples collected for docetaxel pharmacokinetics with and without concomitant prednisone. Plasma docetaxel concentrations were measured with a validated liquid chromatography/mass spectroscopy method (13). Plasma concentration/time data were analyzed with the previously developed population pharmacokinetics Nonlinear Mixed Effect Model (14, 15). No significant differences were observed between mean docetaxel clearance values when docetaxel was administered alone (day 1) or with prednisone (day 22) with either docetaxel dose/schedule.

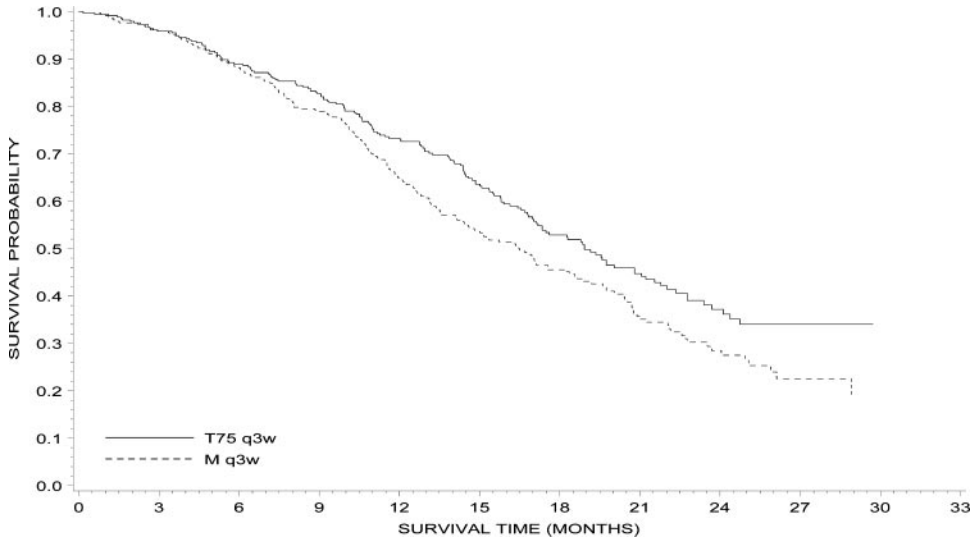

Fig. 2 Overall survival K-M curve TXTq3w *versus* MTZ.

Table 3 Clinically important treatment emergent adverse events

Adverse event	Taxotere 75 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n = 332 (%)		Mitoxantrone 12 mg/m^2 every 3 weeks + prednisone 5 mg twice daily n = 335 (%)	
	Any	G 3/4	Any	G 3/4
Anemia	66.5	4.9	57.8	1.8
Neutropenia	40.9	32.0	48.2	21.7
Thrombocytopenia	3.4	0.6	7.8	1.2
Febrile neutropenia	2.7	N/A	1.8	N/A
Infection	32.2	5.7	20.3	4.2
Epistaxis	5.7	0.3	1.8	0.0
Allergic reactions	8.4	0.6	0.6	0.0
Fluid retention *	24.4	0.6	4.5	0.3
Weight gain *	7.5	0.3	3.0	0.0
Peripheral edema *	18.1	0.3	1.5	0.0
Neuropathy sensory	30.4	1.8	7.2	0.3
Neuropathy motor	7.2	1.5	3.0	0.9
Rash/desquamation	6.0	0.3	3.3	0.6
Alopecia	65.1	N/A	12.8	N/A
Nail changes	29.5	0.0	7.5	0.0
Nausea	41.0	2.7	35.5	1.5
Diarrhea	31.6	2.1	9.6	1.2
Stomatitis/pharyngitis	19.6	0.9	8.4	0.0
Taste disturbance	18.4	0.0	6.6	0.0
Vomiting	16.9	1.5	14.0	1.5
Anorexia	16.6	1.2	14.3	0.3
Cough	12.3	0.0	7.8	0.0
Dyspnea	15.1	2.7	8.7	0.9
Cardiac left ventricular function	9.6	0.3	22.1	1.2
Fatigue	53.3	4.5	34.6	5.1
Myalgia	14.5	0.3	12.8	0.9
Tearing	9.9	0.6	1.5	0.0
Arthralgia	8.1	0.6	5.1	1.2

Abbreviations: G, grade; N/A, not applicable.
* Related to treatment.

Although peak docetaxel concentrations were higher in patients receiving TXT q 3w than those receiving TXT q w, the small sample size of patients with pharmacokinetics evaluation does not allow correlation of peak docetaxel concentrations with efficacy outcomes.

DISCUSSION

Although several single agent and combination regimens have previously indicated antitumor activity in metastatic hormone-refractory prostate cancer and mitoxantrone/prednisone had shown a palliative effect, none have shown a survival benefit in this setting. The results of TAX327 show a survival benefit of docetaxel given with an every 3 weeks schedule plus prednisone in this setting.

The shown survival advantage was noted for the q3 week schedule and was not observed with the weekly docetaxel schedule. As discussed above, the small difference in relative dose intensity between the two docetaxel arms is not likely to provide an adequate explanation for this outcome. One hypothesis is that peak levels (Cmax) achieved on a relatively more intermittent basis may be more relevant to biological activity than overall exposure (area under the curve) in this setting. However, the small sample size of the subset population of TAX327 for which pharmacokinetics data were collected and analyzed precludes our ability to reach any conclusions in this regard.

Preliminary findings of a randomized study comparing docetaxel plus estramustine to mitoxantrone plus prednisone conducted by the Southwest Oncology Group (SWOG9916) also seem to show a survival benefit for a docetaxel-based combination regimen in the treatment of hormone-refractory prostate cancer. A median survival advantage of ~2 months was observed for docetaxel/estramustine compared with the standard arm in this trial, which enrolled 770 patients (16–18).

The findings reported herein provide a rationale for investigating the use of docetaxel in a less advanced and less heavily pretreated population of prostate cancer patients. These results also warrant additional investigation of novel agents in patients with hormone-refractory prostate cancer who have advanced disease and who progress after treatment with docetaxel-based therapy.

CONCLUSIONS

On May 19, 2004, the FDA approved docetaxel for use in combination with prednisone for the treatment of metastatic hormone-refractory prostate cancer based on a survival advantage shown over mitoxantrone plus prednisone in a global, multicenter clinical trial. The recommended dose of docetaxel is 75 mg/m^2 every 3 weeks as a 1-hour infusion. Prednisone 5 mg orally twice a day is administered continuously. This represents the first approval of a chemotherapy regimen for the treatment

of metastatic hormone-refractory prostate cancer based on demonstration of a survival benefit.

REFERENCES

1. Pienta KJ, Sandler H, Javidan J, Sanda MG. Prostate cancer. In: Pazdur R, Coia LR, Hoskins WJ, Wagman LD, editors. Cancer management: a multidisciplinary approach. 7th ed. New York: The Oncology Group; 2003. p. 361–82.

2. Ryan CJ, Small EJ. Advances in prostate cancer. Curr Opin Oncol 2004;16:242–6.

3. Fifty-first meeting of the Oncology Drugs Advisory Committee of FDA; Gaithersburg, Maryland. September 11, 1996.

4. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol 1996;14:1756–64.

5. Picus J, Schultz M. Docetaxel as monotherapy in the treatment of hormone-refractory prostate cancer: preliminary results. Semin Oncol 1999;26(5 Suppl):14–8.

6. Friedland D, Cohen J, Miller R Jr, et al. A Phase II trial of Docetaxel in hormone-refractory prostate cancer: correlation of anti-tumor effect to phosphorylation of Bcl-2. Semin Oncol 1999;26(5 Suppl):19–23.

7. Beer TM, Pierce WC, Lowe BA, et al. Phase II study of weekly Taxotere in symptomatic androgen-independent prostate cancer. Ann Oncol 2001;12:1273–79.

8. Petrioli R, Pozzessere D, Messinese S, et al. Weekly low-dose Taxotere in advanced hormone-refractory prostate cancer subjects previously exposed to chemotherapy. Oncology (Basel) 2003;64:300–5.

9. Berry W, Dakhil S, Gregurich MA, et al. Phase II trial of single-agent weekly Taxotere in hormone-refractory, symptomatic, metastatic carcinoma of the prostate. Semin Oncol 2001;28(15 Suppl):8–15.

10. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800–2.

11. Pichard L, Fabre I, Daujat M, et al. Effect of corticosteroids on the expression of cytochromes P450 and on cyclosporin A oxidase activity in primary cultures of human hepatocytes. Molecular Pharm 1992;41: 1047–55.

12. Marre F, Sanderink GJ, de Sousa G, et al. Hepatic biotransformation of docetaxel (Taxotere) in vitro: involvement of the CYP3A subfamily in humans. Cancer Res 1996;56:1296–302.

13. Wang LZ, Goh BC, Grigg ME, et al. A rapid and sensitive liquid chromatography/tandem mass spectrometry method for determination of docetaxel in human plasma. Rapid Commun Mass Spectrom 2003;17: 1548–52.

14. Bruno R, Hille D, Riva A, et al. Population pharmacokinetics/ pharmacodynamics (PK/PD) of docetaxel in phase 2 studies in subjects with cancer. J Clin Oncol 1998;16:187–96.

15. Bruno R, Vivier N, Veyrat-Follet C, Montay G, Rhodes GR. Population pharmacokinetics and pharmacokinetic-pharmacodynamic relationships for docetaxel. Investig New Drugs 2001;19:163–9.

16. Hussain M, Petrylak D, Fisher E, Tangen C, Crawford D. Docetaxel and estramustine versus mitoxantrone and prednisone for hormone-refractory prostate cancer: scientific basis and design of Southwest Oncology Group Study 9916. Semin Oncol 1999;26(5 Suppl 17):55–60.

17. Petrylak DP, Tangen C, Hussain M, et al. SWOG 99–16: randomized phase III trial of docetaxel/estramustine versus mitoxantrone/prednisone in men with androgen-independent prostate cancer [abstract 3, plenary session]. Am Soc Clin Oncol Proc 2004.

18. Petrylak DP. Examination of end points in the SWOG Docetaxel trial. Prostate Cancer Endpoints Workshop; Bethesda, Maryland. June 22, 2004.