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Association of Survival Benefit With Docetaxel in Prostate Cancer and Total Number of Cycles Administered
A Post Hoc Analysis of the Mainsail Study

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IMPORTANCE The optimal total number of docetaxel cycles in patients with metastatic castration resistant prostate cancer (mCPRC) has not been investigated yet. It is unknown whether it is beneficial for patients to continue treatment upon 6 cycles.

OBJECTIVE To investigate whether the number of docetaxel cycles administered to patients deriving clinical benefit was an independent prognostic factor for overall survival (OS) in a post hoc analysis of the Mainsail trial.

DESIGN, SETTING, AND PARTICIPANTS The Mainsail trial was a multinational randomized phase 3 study of 1059 patients with mCRPC receiving docetaxel, prednisone, and lenalidomide (DPL) or docetaxel, prednisone, and a placebo (DP). Study patients were treated until progressive disease or unacceptable adverse effects occurred. Median OS was found to be inferior in the DPL arm compared with the DP arm. As a result of increased toxic effects with the DPL combination, patients on DPL received fewer docetaxel cycles (median, 6) vs 8 cycles in the control group. As the dose intensity was comparable in both treatment arms, we investigated whether the number of docetaxel cycles administered to patients deriving clinical benefit on Mainsail was an independent prognostic factor for OS. We conducted primary univariate and multivariate analyses for the intention-to-treat population. Additional sensitivity analyses were done, excluding patients who stopped treatment for reasons of disease progression and those who received 4 or fewer cycles of docetaxel for other reasons, minimizing the effect of confounding factors.

MAIN OUTCOMES AND MEASURES Total number of docetaxel cycles delivered as an independent factor for OS.

RESULTS Overall, all 1059 patients from the Mainsail trial were included (mean [SD] age, 68.7 [7.89] years). Treatment with 8 or more cycles of docetaxel was associated with superior OS (hazard ratio [HR], 1.909; 95% CI, 1.660-2.194; $P < .001$), irrespective of lenalidomide treatment (HR, 1.060; 95% CI, 0.924-1.215; $P = .41$). Likewise, in the sensitivity analysis, patients who received a greater number of docetaxel cycles had superior OS; patients who received more than 10 cycles had a median OS of 33.0 months compared with 26.9 months in patients treated with 8 to 10 cycles; and patients who received 5 to 7 cycles had a median OS of 22.8 months ($P < .001$).

CONCLUSIONS AND RELEVANCE These findings suggest that continuation of docetaxel chemotherapy contributes to the survival benefit. Prospective validation is warranted.

Supplemental content

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Docetaxel combined with prednisone is the current first line chemotherapy for metastatic castration resistant prostate cancer (mCRPC). In the TAX 327 registration trial,[1] the number of 10 cycles of docetaxel every 3 weeks was arbitrarily chosen, and the median number actually delivered was 9.5. In study SWOG 99-16,[2] patients were scheduled to receive a maximum of 12 cycles. To date, the optimal number of docetaxel cycles has not been established. Prospective clinical trials to improve upon docetaxel have generally focused on the addition of a second active agent. In these trials the number of cycles has been arbitrarily set at 10 to 12 cycles or until disease progression or unacceptable adverse effects occurred. Outside the context of clinical trials—especially following the recent advent of novel androgen receptor (AR)-targeted agents, including abiraterone and enzalutamide—docetaxel chemotherapy, either for convenience, or to avoid cumulative side effects, is often and increasingly halted at 6 cycles.[3]

The Mainsail study[4] (NCT00988208) investigated the safety and efficacy of the addition of lenalidomide, an antiangiogenic agent with immunomodulatory properties, to docetaxel plus prednisone in a randomized double-blind placebo-controlled phase 3 clinical trial. The study was stopped early due to a futility analysis, in which the median overall survival (OS) of docetaxel and prednisone plus lenalidomide (DPL) was inferior to docetaxel and prednisone plus placebo (DP). The addition of lenalidomide to docetaxel increased the toxic effects of the regimen, including increased myelotoxic effects, and caused more frequent docetaxel dose reductions and eventually fewer cycles administered. The dose adjustment protocol for myelotoxic effects specified that reductions were primarily made in the docetaxel dose. The study protocol mandated continuation of treatment (docetaxel and lenalidomide, or placebo) until radiographic disease progression or unacceptable adverse effects occurred. The median number of cycles delivered in the experimental arm was 6, whereas the patients in the control arm received a median of 8 cycles. Since the dose intensity per cycle was comparable in both treatment arms (94.4% in the DPL arm and 95.6% in the DP arm), we investigated whether the difference in OS could be attributed to the cumulative dose as reflected by the total number of docetaxel cycles administered.

Key Points

Question Is the total number of docetaxel cycles administered to patients with metastatic castration resistant prostate cancer an independent prognostic factor for overall survival (OS)?

Findings In a post hoc analysis of the Mainsail study, it was found that the total number of docetaxel cycles delivered is an independent factor for OS. Patients who received more than 10 cycles of docetaxel had a higher median OS compared with patients treated with 8 to 10 cycles or patients treated with 5 to 7 cycles.

Meaning These findings suggest that the total number of docetaxel cycles administered to patients with metastatic castration resistant prostate cancer contributes to OS.

Methods

Study Design and Patients

Mainsail[4] was a randomized, double-blind, placebo-controlled phase 3 study, conducted at 223 centers in the United States, Canada, Europe, Russia, Australia, South Africa, Israel, and Mexico, accruing 1059 patients. The study was initiated in November 2009 and was ended early in November 2011 because of futility. Full details are provided in the original report.[4] Patients with mCRPC who were chemotherapy-naive were eligible for inclusion if they met the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or less; hemoglobin level more than 9 g/dL (to convert g/dL to g/L, multiply by 10.0); absolute neutrophil count more than 1.5×10^9/L; platelet count more than 100×10^9/L; creatinine clearance level more than 50 mL/min; total bilirubin level less than 1.0 × upper limit of normal (ULN); serum aspartate transaminase and alanine transaminase levels less than 1.5 × ULN; alkaline phosphatase level less than 2.5 × ULN. Effective castration was defined as serum testosterone levels less than 50 ng/dL (to convert ng/dL to nmol/L, multiply by 0.0347). Patients were randomized 1:1 to docetaxel (75 mg/m^2) and prednisone plus lenalidomide 25 mg/d (DPL) or docetaxel plus prednisone and placebo (DP) on days 1 through 14. Patients were stratified by baseline ECOG performance status, geographic region and type of progressive disease (rising prostate-specific antigen [PSA] levels vs tumor progression). Patients were kept on protocol treatment until disease progression or until unacceptable adverse effects occurred. In case of hematologic toxic effects (eg, febrile neutropenia or grade 4 neutropenia lasting more than 1 week) and certain nonhematologic toxic effects (eg, grade >3 cutaneous reactions or moderate neurosensory symptoms), dose reductions were primarily made for docetaxel. The primary end point of the study was OS, defined as time from randomization to death.

Statistical Analyses

Our primary analysis was an intention-to-treat (ITT) analysis on overall survival (OS) for the entire data set updated by March 15, 2016, using the Kaplan-Meier method and Cox proportional hazard model. We conducted univariate and multivariate analyses including the following parameters: treatment group (DPL or DP); baseline PSA level; baseline lactate dehydrogenase [LDH] level; baseline total testosterone; number of treatment cycles; duration of lenalidomide or placebo; baseline hemoglobin; baseline albumin; age; baseline ECOG performance status; baseline body mass index (BMI; calculated as weight in kilograms divided by height in meters squared); prior treatments; baseline creatinine clearance; geographic region; and race group. To reduce the potential bias of stopping docetaxel owing to disease progression and associated potential confounding effect on survival, we performed additional sensitivity analyses. The sensitivity analyses excluded patients who had stopped docetaxel due to disease progression, or had received less than a minimum of 5 cycles, since it was felt that patients who had been exposed to docetaxel for only a

Table 1. Baseline Patient Demographics and Characteristics

Characteristic	No. (%) DPL (n = 553) ≥8 Cycles (n = 275)	DPL (n = 553) <8 Cycles (n = 258)	DP (n = 526) ≥8 Cycles (n = 332)	DP (n = 526) <8 Cycles (n = 194)	Total (n = 1059)
Age, No., y					
Mean (SD)	67.5 (7.39)	70.5 (8.30)	68.3 (7.17)	68.8 (8.77)	68.7 (7.89)
Median (range)	67.9 (43-88)	71.3 (45-89)	68.1 (51-87)	69.8 (47-90)	69.0 (43-90)
Q1-Q3	62.5-73.0	65.9-76.1	63.6-73.6	63.5-74.5	63.8-74.4
IQR	10.5	10.2	10.0	11.0	10.6
Age category, y					
<65	107 (38.9)	56 (21.7)	109 (32.8)	62 (32.0)	334 (31.5)
65-≤75	128 (46.5)	116 (45.0)	156 (47.0)	90 (46.4)	490 (46.3)
>75	40 (14.5)	86 (33.3)	67 (20.2)	42 (21.6	235 (22.2)
Race/ethnicity					
American Indian or Alaskan	2 (0.7)	1 (0.4)	2 (0.6)	3 (1.5)	8 (0.8)
Native	3 (1.1)	3 (1.2)	4 (1.2)	4 (2.1)	14 (1.3)
Asian	8 (2.9)	13 (5.0)	12 (3.6)	13 (6.7)	46 (4.3)
Black or African American	223 (81.1)	213 (82.6)	275 (82.8)	158 (81.4)	869 (82.1)
White	39 (14.2)	28 (10.9)	39 (11.7)	16 (8.2)	122 (11.5)
Other or no answer					
Sex					
Male	275 (100)	258 (100)	332 (100)	194 (100)	1059 (100)
ECOG Score					
O to 1	268 (97.5)	240 (93.0)	321 (96.7)	183 (94.3)	1012 (95.6)
= 0	142 (51.6)	110 (42.6)	163 (49.1)	94 (48.5)	509 (48.1)
= 1	126 (45.8)	130 (50.4)	158 (47.6)	89 (45.9)	503 (47.5)
= 2	6 (2.2)	18 (7.0)	11 (3.3)	10 (5.2)	45 (4.2)
= 3	0	0	0	1 (0.5)	1 (0.1)
Not specified	1 (0.4)	0	0	0	1 (0.1)
Region					
United States or Canada	64 (23.3)	76 (29.5)	75 (22.6)	61 (31.4)	276 (26.1)
European Union or Australia	180 (65.5)	150 (58.1)	215 (64.8)	114 (58.8)	659 (62.2)
Rest of world	31 (11.3)	32 (12.4)	42 (11.7)	19 (9.8)	124 (11.7)
Previous disease progression					
Chronic renal failure	80 (29.1)	79 (30.6)	94 (28.3)	52 (26.8)	305 (28.8)
Rising PSA only	195 (70.9)	179 (69.4)	238 (71.7)	142 (73.2)	754 (71.2)
Radiographic progression[a]					
Prior radiation therapy					
Yes	153 (55.6)	159 (61.6)	196 (59.0)	112 (57.7)	620 (58.5)
No	122 (44.4)	99 (38.4)	136 (41.0)	82 (42.3)	439 (41.5)
Prior cancer surgeries					
Yes	190 (69.1)	168 (65.1)	209 (63.0)	126 (64.9)	693 (65.4)
No	85 (30.9)	90 (34.9)	123 (37.0)	68 (35.1)	366 (34.6)
Prior hormonal anticancer therapies					
Yes	261 (94.9)	250 (96.9)	323 (97.3)	189 (97.4)	1023 (96.6)
No[b]	14 (5.1)	8 (3.1)	9 (2.7)	5 (2.6)	36 (3.4)
Other prior anticancer therapies					
Yes	34 (12.4)	37 (14.3)	52 (15.7)	27 (13.9)	150 (14.2)
No	241 (87.6)	221 (85.7)	280 (84.3)	167 (86.1)	909 (85.8)
Baseline PSA levels, ng/ml					
No.	274	257	330	192	1053
Mean (SD)	302.421 (810.7726)	331.512 (738.6567)	282.001 (599.0856)	304.552 (752.7563)	303.542 (720.2895)
Median (range)	98.200 (0.21-10 759)	114.000 (0.10-8665)	84.000 (0.33-6807)	87.850 (0.01-5715)	95.200 (0.01-10 759)
Q1, Q3	32.200, 264.000	34.900, 339.000	31.000, 275.000	33.650, 253.000	32.800, 283.000
IQR	231.800	304.100	244.000	219.350	250.200

(continued)

Table 1. Baseline Patient Demographics and Characteristics

Characteristic	No. (%) DPL (n = 553) ≥8 Cycles (n = 275)	DPL (n = 553) <8 Cycles (n = 258)	DP (n = 526) ≥8 Cycles (n = 332)	DP (n = 526) <8 Cycles (n = 194)	Total (n = 1059)
Metastatic sites (other than prostate)					
Bone only	84 (30.5)	85 (32.9)	100 (30.1)	100 (30.1)	326 (30.8)
Soft tissues only	52 (18.9)	52 (20.2)	58 (17.5)	58 (17.5)	198 (18.7)
Both bone and soft tissues	138 (50.2)	121 (46.9)	173 (52.1)	173 (52.1)	532 (50.2)
None	1 (0.4)	0	1 (0.3)	1 (0.3)	3 (0.3)

Abbreviations: BMI, Body mass index (calculated as weight in kilograms divided by height in meters squared); DP, docetaxel, prednisone, and placebo; DPL, docetaxel, prednisone, and lenalidomide; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PSA, prostate-specific antigen.

[a] Any patient enrolling in the study with evidence of radiographic progression was stratified into the radiographic progression strata regardless of PSA status.

[b] All patients had either prior bilateral orchiectomy or ongoing androgen blockage.

few cycles were not likely to obtain a meaningful survival benefit from the chemotherapy. Final multivariate model was selected by stepwise procedure from the proportional hazard model.

Results

Baseline Characteristics

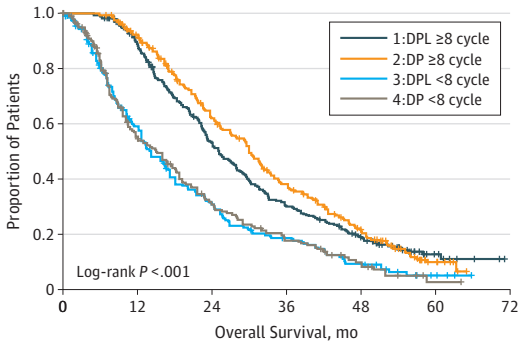
The ITT analysis included all 1059 randomized patients. The baseline characteristics are shown in **Table 1**. In the DPL arm 244 patients received 8 or more cycles of docetaxel and 289 patients received less than 8 cycles of docetaxel. In the DP arm, 296 patients received 8 or more cycles of docetaxel and 230 patients received fewer than 8 cycles docetaxel. For the sensitivity analysis, 250 patients were excluded because they had received 4 or fewer cycles of docetaxel, and 264 patients were excluded who had stopped docetaxel due to disease progression (of which, 60 patients also received ≤4 cycles). Data were analyzed using several cutoff points; 5 to 7 vs 8 to 10 cycles and 10 or fewer vs more than 10 cycles. In the sensitivity analysis, patients in the DPL and the DP arm were tested separately as well as grouped together. Hence, 605 patients who had not stopped docetaxel due to disease progression and who had a minimum exposure of 5 cycles were included in this analysis (eFigure 1 in the Supplement).

Overall Survival Based on Number of Docetaxel Cycles

The analysis on the ITT population showed a robust superior OS for patients treated with a greater number of cycles. We examined the number of docetaxel cycles by using 6, 8, and 10 or more as cutoff points, as well as the number of cycles as continuous variable. **Figure 1** shows the OS for patients in the subgroups receiving 8 or more cycles vs those receiving less than 8 cycles for both the DPL and DP arms. Identical findings were obtained for 6 or more cycles vs less than 6 cycles and 10 or more cycles vs less than 10 cycles (eFigure 2 and eFigure 3 in the Supplement).

As previously reported, the DPL arm showed a significantly inferior survival compared with the DP arm. In the univariate analysis, the number of treatment cycles (as continuous variable) ($P < .001$), the cumulative dose of docetaxel ($P < .001$), the duration of lenalidomide ($P < .001$), and the allocated treatment arm ($P = .03$) were all significant (**Table 2**). In the multivariate model, not taking into account the number of cycles as a variable, the treatment arm was statistically significant (hazard ratio (HR), 1.626; 95% CI, 1.237-2.13; $P < .001$). However, when the number of cycles (<8 vs ≥8) was included in the multivariate analysis, the number of docetaxel cycles was a statistically significant independent factor affecting OS (HR, 1.909; 95% CI, 1.660-2.194; $P < .001$), but the treatment arm (DPL vs DP) was not retained (HR, 1.060; 95% CI, 0.924-1.215; $P = .41$). This implies that the cumulative dose of

Figure 1. Overall Survival for DP and DPL Arms



No. at risk

1:DPL ≥8 cycle	275	232	136	77	44	8
2:DP ≥8 cycle	332	295	189	111	55	11
3:DPL <8 cycle	258	131	67	39	18	4
4:DP <8 cycle	194	96	50	28	10	1

	No. of Participants	Event	Censored	Median Survival Time, mo	Survival (95% CI)
1:DPL ≥8 cycle	275	221 (80%)	54 (20%)	25.0	(23.0-27.9)
2:DP ≥8 cycle	332	264 (80%)	68 (20%)	29.8	(27.8-32.1)
3:DPL <8 cycle	258	213 (83%)	45 (17%)	14.2	(12.7-16.8)
4:DP <8 cycle	194	159 (82%)	35 (18%)	15.0	(11.5-18.3)

Kaplan-Meier plots of overall survival for the DP (docetaxel, prednisone) and the DPL (docetaxel, prednisone, and lenalidomide) arm in the subgroups of the less than 8 vs 8 or more docetaxel cycles for the the intention-to-treat population. An event indicates a death.

Table 2. Multivariate Cox Regression Model on Overall Survival for the Intention-to-Treat Population

Variables	Univariate, Hazard Ratio (95% CI)	*P* Value	Multivariate, Hazard Ratio (95% CI)	*P* Value
Treatment group, DP vs DPL	1.158 (1.013-1.324)	.032	1.060 (0.924-1.215)	.41
Baseline PSA for every 100 ng/ml increase	1.015 (1.008-1.021)	<.001	...	...
Baseline LDH, for every 50 U/L increase	1.102 (1.089-1.116)	<.001	1.077 (1.063-1.092)	<.001
Number of treatment cycles for each cycle increase	0.930 (0.917-0.943)	<.001	...	...
Number of treatment cycles for <8 vs ≥8	1.933 (1.687-2.214)	<.000	1.909 (1.660-2.194)	<.001
Duration of lenalidomide or placebo, for each week increase	0.985 (0.981-0.989)	<.001	...	...
Cumulative dose of docetaxel, for each 10 mg/m^2 increase	0.990 (0.988-0.993)	<.001	...	...
Baseline HGB for each g/dL increase	0.789 (0.753-0.826)	<.001	0.887 (0.842-0.935)	<.001
HGB, ≤10 vs >10 cycles	2.270 (1.771-2.910)	<.001	...	...
Baseline value of albumin, for each g/L increase	0.906 (0.888-0.924)	<.001	0.947 (0.926-0.968)	<.001
Age, y				
<65 vs >75	0.779 (0.648-0.935)	.01	...	...
65-75 vs >75	0.784 (0.660-0.930)	.01	...	...
Baseline ECOG group, high (2, 3) vs low (0, 1)	2.639 (1.944-3.583)	<.001	1.797 (1.300-2.485)	<.001
Baseline BMI for each unit increase	0.985 (0.971-1.000)	.04	...	...
Prior cancer surgery, no vs yes	1.096 (0.952-1.261)	.20	...	...
Prior hormonal anticancer therapy, no vs yes	0.870 (0.584-1.295)	.49	...	...
Prior radiation therapy, no vs yes	0.999 (0.872-1.145)	.99	...	...
Baseline creatinine clearance for each unit increase	0.999 (0.996-1.002)	.67	...	...
Region				
European Union and Australia vs United States and Canada	1.000 (0.857-1.167)	>.99	...	...
Rest of world vs United States/Canada	1.105 (0.847-1.441)	.46	...	...
Race/ethnicity				
Black or African American vs white	1.087 (0.774-1.526)	.63	...	...
Other vs white	0.950 (0.782-1.155)	.60	...	...

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DP, docetaxel, prednisone, and placebo; DPL, docetaxel, prednisone, and lenalidomide; ECOG, Eastern Cooperative Oncology Group; HGB, hemoglobin; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; ellipses, not applicable or no data available.

docetaxel, as reflected by the total number of cycles administered, is an independent factor for OS. Other well-known predictors such as baseline LDH ($P < .001$), baseline albumin ($P < .001$), baseline hemoglobin ($P < .001$), and baseline ECOG Performance Status ($P < .001$) were significant independent contributors of OS following docetaxel treatment.

In the sensitivity analysis, we investigated whether the number of docetaxel cycles administered to patients continuing treatment beyond 4 cycles and not stopping due to disease progression was an independent prognostic factor for OS. Treatment arm was not a significant factor affecting survival in either the univariate or the multivariate analysis (**Table 3**). Patients who had received 10 or more cycles of docetaxel had the greatest median OS of 33.0 months, compared with those who received 8 to 10 cycles (26.9 months) or 5-7 cycles (22.8 months) when treatment groups were combined ($P < .001$) (**Figure 2**). The same holds true when the arms were analyzed separately (eFigure 4 in the Supplement): in the DPL arm, median OS for patients receiving more than 10 cycles, 8 to 10 cycles, and 5 to 7 cycles of docetaxel was 31.6, 24.4, and 18.8 months, respectively; in the DP arm, median OS for patients receiving more than 10 cycles, 8 to 10 cycles, and 5 to 7 cycles of docetaxel was 34.7, 29.7, and 23.6 months, respectively ($P < .001$). All comparisons for OS between the cohorts receiving 5 or 6, vs more 6 cycles, 5 to 7 vs 8 to 10 cycles, and 8 to 10 vs more than 10 cycles of docetaxel, and cumulative dose of docetaxel, were significant in the univariate model. The cutoff 5 or 6 cycles of docetaxel vs more than 6 cycles had the strongest independent significance and was thus retained in the multivariate model. The established contributors for OS—baseline LDH ($P < .001$), baseline hemoglobin ($P = .006$), baseline albumin ($P = .006$) and baseline ECOG Performance Status ($P = .03$)—also had independent significance and were retained in the multivariate model (Table 3).

Discussion

Mainsail[4] is one of the largest phase 3 trials in the setting of mCRPC in the past decade that investigated the addition of a second active biological drug to standard docetaxel every 3 weeks plus prednisone. In Mainsail the greater myelotoxic

Table 3. Multivariate Cox Regression Model on Overall Survival for Patients Who Underwent 5 or More Cycles of Docetaxel

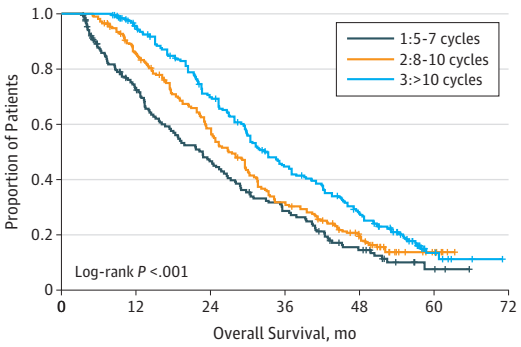
Variables	Univariate, Hazard Ratio (95% CI)	*P* Value	Multivariate, Hazard Ratio (95% CI)	*P* Value
Treatment group, DP vs DPL	1.089 (0.908-1.305)	.36	1.014 (0.843-1.220)	.88
Baseline PSA for every 100 ng/ml increase	1.014 (1.006-1.022)	<.001		
Baseline LDH, for every 50 U/L increase	1.134 (1.107-1.162)	<.001	1.113 (1.085-1.142)	<.001
Number of treatment cycles for each cycle increase	0.945 (0.924-0.966)	<.001	...	...
Treatment cycles, No.				
5-6 vs >6	1.447 (1.139-1.839)	.001	1.383 (1.085-1.763)	.01
5-7 vs 8-10	1.279 (1.014-1.615)	.04	...	...
8-10 vs >10	1.340 (1.085-1.656)	.001	...	...
Duration of lenalidomide or placebo, for each week increase	0.991 (0.985-0.997)	.002	...	...
Cumulative dose of docetaxel, for each 10 mg/m^2 increase	0.994 (0.991-0.998)	.001	...	...
Baseline HGB for each g/dL increase	0.815 (0.766-0.868)	<.001	0.902 (0.838-0.971)	.01
HGB, ≤10 vs >10 cycles	2.348 (1.644-3.353)	<.001	...	...
Baseline value of albumin, for each g/L increase	0.917 (0.892-0.943)	<.001	0.957 (0.927-0.987)	.01
Age, y				
<65 vs >75	0.728 (0.566-0.936)	.01	...	...
65-75 vs >75	0.779 (0.617-0.982)	.03	...	...
Baseline ECOG group, high (2, 3) vs low (0, 1)	2.429 (1.447-4.078)	<.001	1.825 (1.063-3.133)	.03
Baseline BMI for each unit increase	0.993 (0.973-1.013)	.46	...	...
Prior cancer surgery, no vs yes	1.086 (0.897-1.316)	.40	...	...
Prior hormonal anticancer therapy, no vs yes	0.848 (0.478-1.505)	.57	...	...
Prior radiation therapy, no vs yes	0.988 (0.821-1.188)	.90	...	...
Baseline creatinine clearance for each unit increase	1.000 (0.996-1.004)	.96	...	...
Region				
European Union and Australia vs United States and Canada	1.028 (0.828-1.275)	.80	...	...
Rest of world vs United States/Canada	1.264 (0.876-1.822)	.21	...	...
Race/ethnicity				
Black or African American vs white	0.703 (0.396-1.249)	.22	...	...
Other vs white	0.991 (0.759-1.293)	.95	...	...

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DP, docetaxel, prednisone, and placebo; DPL, docetaxel, prednisone, and lenalidomide; ECOG, Eastern Cooperative Oncology Group; HGB, hemoglobin; LDH, lactate dehydrogenase; PSA, prostate-specific antigen; ellipses, not applicable or no data available.

effect caused by the addition of lenalidomide to docetaxel resulted in a reduction of the number of cycles of docetaxel that patients were able to tolerate, a median of 6 cycles in the DPL arm vs 8 in the DP arm. Median OS was shorter in patients receiving lenalidomide, which could have attributed to either a direct adverse effect of lenalidomide on OS or alternatively because of the reduction in the number of docetaxel treatment cycles. In this study we investigated the effect of the cumulative dose of docetaxel as reflected by the total number of cycles of docetaxel on median OS, in univariate and multivariate analyses on the ITT population, both dependent upon the treatment arm, as well as irrespective of the treatment arm. In subsequent sensitivity analyses we addressed potential confounding factors on the eventual survival outcome, such as disease progression as the main reason for stopping docetaxel treatment, and excluding patients from the analysis who received less than a minimum of 5 cycles for whom meaningful survival benefit due to docetaxel was questionable and could therefore bias the analysis.

We found that the total number of docetaxel cycles delivered was an independent and important contributor to the OS benefit provided by docetaxel chemotherapy that was independent of known prognostic factors for survival, including performance (ECOG score), baseline LDH, baseline hemoglobin, and baseline albumin.[5] Patients in the Mainsail study[4] had been treated according to a strict protocol, mandating continuation of the allocated treatment until documented disease progression or until unacceptable adverse effects occurred. In the sensitivity analysis we corrected for confounding factors, including disease progression, as the reason for stopping docetaxel, though the main reason for stopping protocol treatment early was adverse effects. Enhanced toxic effects by the addition of lenalidomide to docetaxel in the experimental arm resulted in a lower cumulative dose of docetaxel, reflected by fewer docetaxel cycles admin-

Figure 2. Overall Survival for Patients Who Underwent More Than 4 Cycles of Chemotherapy



No. at risk

1:5-7 cycles	154	101	63	38	17	3
2:8-10 cycles	213	177	115	63	31	6
3:>10 cycles	238	215	151	94	55	9

	No. of Participants	Event	Censored	Median Survival Time, mo	Survival (95% CI)
1:5-7 cycles	154	122 (79%)	32 (21%)	22.8	(17.6-26.6)
2:8-10 cycles	213	169 (79%)	44 (21%)	26.9	(24.1-30.1)
3:>10 cycles	238	178 (75%)	60 (25%)	33.0	(29.9-37.2)

Kaplan-Meier plots of overall survival in the subgroups of 5 to 7, 8 to 10 cycles, and more than 10 docetaxel cycles. The DP (docetaxel, prednisone, and placebo) and DPL (docetaxel, prednisone, and lenalidomide) treatment arms are combined; patients with progressive disease and/or 4 or fewer cycles of docetaxel were excluded from the analysis. An event indicates a death.

istered and more frequent dose reductions. Because the median dose achieved per cycle administered was only modestly affected (respectively of the planned dose: 94.4% in the DPL arm and 95.6% in the DP arm), the number of cycles delivered was the key contributor to the different survival outcome.[4] Our data strongly suggest that the difference in the cumulative docetaxel exposure caused the worse OS in the experimental arm. These findings imply that the total dose of docetaxel, as reflected in total the number of cycles achieved, contributes to the eventual survival gain by chemotherapy in the patient population with mCRPC.

This finding has important implications for the optimal administration of docetaxel chemotherapy. To provide the greatest survival gain by docetaxel chemotherapy, those patients who appear to benefit by clinical or radiological evidence and who tolerate the chemotherapy well should continue beyond 6, and perhaps even beyond 10 cycles, until disease progression occurs or unacceptable adverse effects dictate otherwise.

An obvious limitation of this study is the post hoc nature of the analysis. Although all patients were treated according to the strict Mainsail study protocol,[4] some patients may have discontinued for reasons not fully reflected in the study case report file. Subtle changes in PSA levels that may influence treatment decisions in daily clinical practice are less likely to have occurred in the context of a strict protocol, as evidenced by the observation that more than 50% of the patients continued treatment beyond 8 cycles. In addition, such potential unrecognized cessation of docetaxel treatment for nonspecified reasons is not likely to have a meaningful confounding effect given the sample size of the study and the robustness and consistency of the data. We conducted both an ITT analysis and sensitivity analysis, and all analyses point in the same direction. Of note, the number of cycles was independent of the performance score and other known prognostic factors for survival. In 2010 and subsequent years, additional treatment options have become available in the post-docetaxel setting, including cabazitaxel,[6] abiraterone,[7,8] enzalutamide,[9,10] and radium-223.[11] It is conceivable that many patients after ending treatment in the Mainsail study received at least 1 additional line of treatment. Unfortunately, no information on poststudy treatment was collected in the Mainsail database. We have no reason to anticipate any meaningful imbalance in post-docetaxel treatments between the groups, since the gap between halting docetaxel chemotherapy at 6 or 8 cycles and continuing additional cycles will be limited to a time gap of only a few months.

A prospective study directly comparing 6 vs 10 cycles or beyond 10 cycles would be required to prove a survival benefit of docetaxel continuation. Barriers to conducting such a study would include higher neurological and extramedullary toxic effects expected with higher cumulative doses, higher costs, and the robust findings of this present retrospective analysis. A similar question is what is the optimal number of docetaxel cycles in patients with metastatic hormone sensitive prostate cancer. In 2 pivotal studies, the survival benefit by the early use of docetaxel has been obtained with 6 cycles,[12,13] while in the GETUG trial[14] 9 doses of docetaxel were mandated. In the metastatic hormone sensitive prostate cancer setting, a study of 6 vs 10 cycles would help to answer that question.

Conclusions

We found a robust and independent effect on OS by the number of docetaxel cycles administered in the setting of mCRPC. These data indicate that patients who appear to have clinical, radiological, or biochemical benefit by docetaxel should continue beyond 6 cycles as long as they tolerate their treatment well. A prospective study, potentially in the setting of mHSPC, may lend further prospective evidence.

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REFERENCES

1. Tannock IF, de Wit R, Berry WR, et al; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.

2. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med*. 2004;351(15):1513-1520.

3. Sonpavde G, Bhor M, Hennessy D, et al. Sequencing of cabazitaxel and abiraterone acetate after docetaxel in metastatic castration-resistant prostate cancer: treatment patterns and clinical outcomes in multicenter community-based US oncology practices. *Clin Genitourin Cancer*. 2015;13(4):309-318.

4. Petrylak DP, Vogelzang NJ, Budnik N, et al. Docetaxel and prednisone with or without lenalidomide in chemotherapy-naive patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol*. 2015;16(4):417-425.

5. Halabi S, Lin CY, Kelly WK, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2014;32(7):671-677.

6. de Bono JS, Oudard S, Ozguroglu M, et al; TROPIC Investigators. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet*. 2010;376(9747):1147-1154.

7. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.

8. de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.

9. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.

10. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.

11. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.

12. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163-1177.

13. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737-746.

14. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(2):149-158.