

Supplementary Online Content

de Morrée ES, Vogelzang NJ, Petrylak DP, et al. Association of survival benefit with docetaxel in prostate cancer and total number of cycles administered: a post hoc analysis of the Mainsail study. *JAMA Oncol*. Published online August 25, 2016. doi:10.1001/jamaoncol.2016.3000.

eFigure 1. Overview of the patients included in the analysis

eFigure 2. Kaplan-Meier plots of overall survival for the DP and the DPL arm in the subgroups of number of docetaxel cycles <6 and ≥ 6

eFigure 3. Kaplan-Meier plots of overall survival for the DP and the DPL arm in the subgroups of number of docetaxel cycles <10 and ≥ 10

eFigure 4. Kaplan-Meier plots of overall survival for patients in the docetaxel prednisone and placebo (DP) and docetaxel prednisone and lenalidomide (DPL) arm. (Subgroups 5-7 cycles, 8-10 cycles and > 10 cycles of docetaxel)

eAppendix. Protocol summary

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplementary data

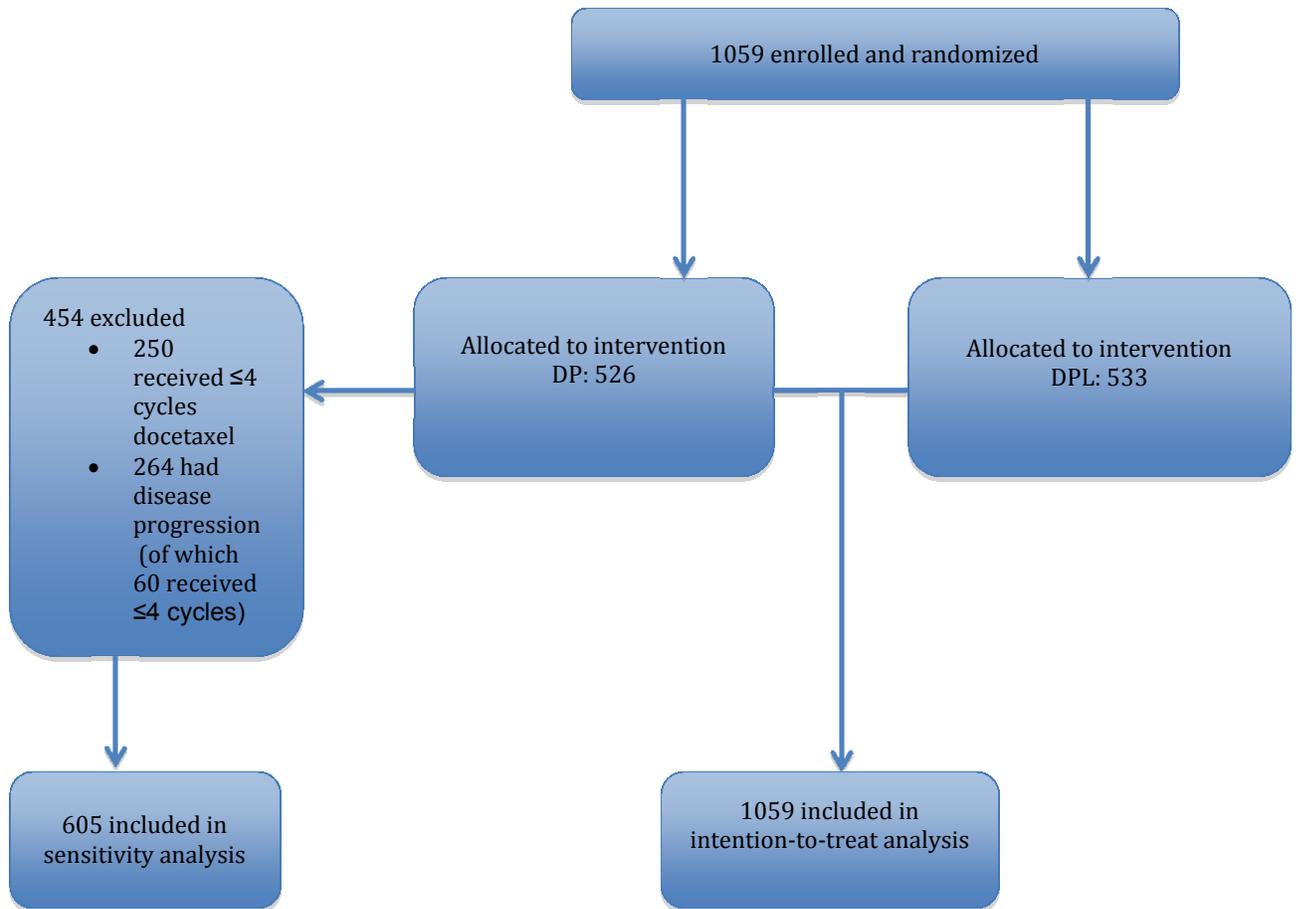
Supplementary figure 1: Overview of the patients included in the analysis

Supplementary figure 2: Kaplan-Meier plots of overall survival for the DP and the DPL arm in the subgroups of number of docetaxel cycles <6 and ≥ 6 .

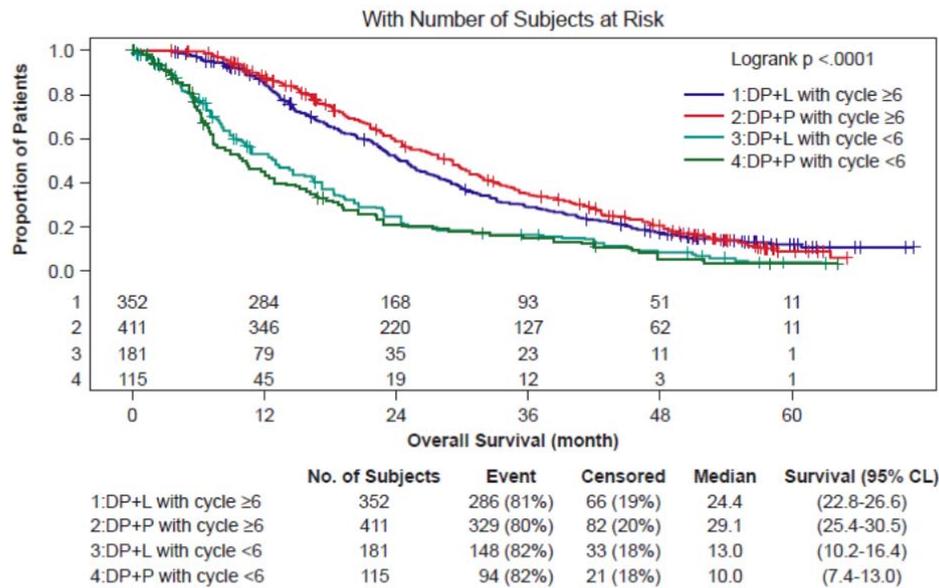
Supplementary figure 3: Kaplan-Meier plots of overall survival for the DP and the DPL arm in the subgroups of number of docetaxel cycles <10 and ≥ 10 .

Supplementary figure 4: Kaplan-Meier plots of overall survival for patients in the docetaxel prednisone and placebo (DP) and docetaxel prednisone and lenalidomide (DPL) arm. (Subgroups 5-7 cycles, 8-10 cycles and > 10 cycles of docetaxel).

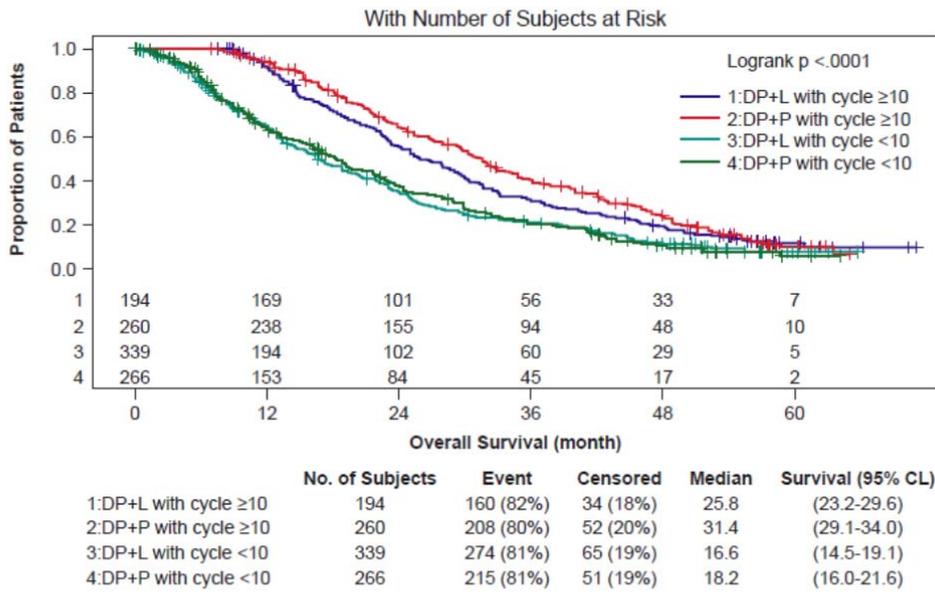
Supplementary file: Protocol summary



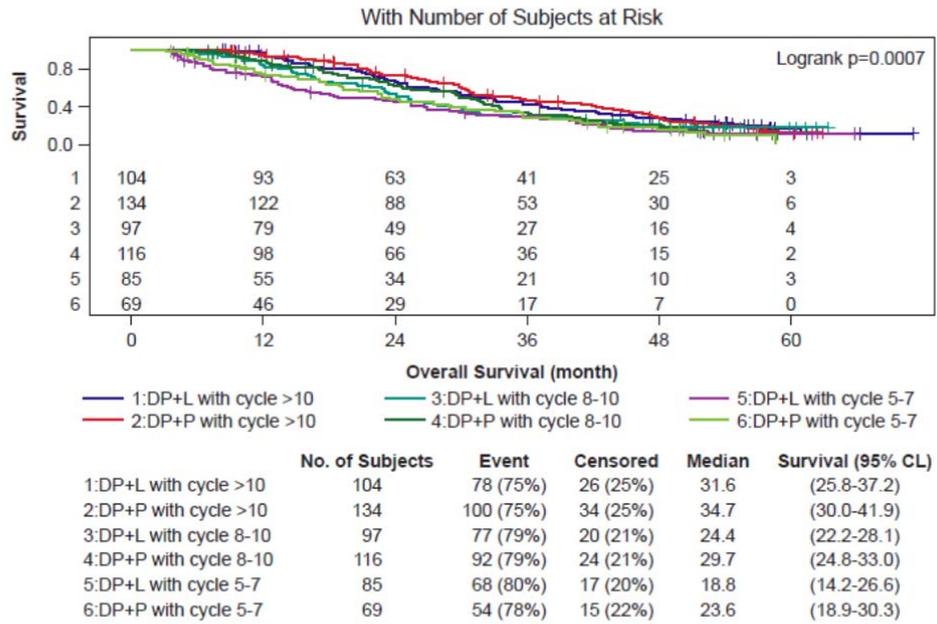
Supplementary figure 1: Overview of the patients included in the analysis. DP: docetaxel, prednisone and placebo; DPL: docetaxel, prednisone and lenalidomide; ITT: intention to treat



Supplementary figure 2: Kaplan-Meier plots of overall survival for the DP (docetaxel, prednisone and placebo) and the DPL (docetaxel, prednisone, lenalidomide) arm in the subgroups of number of docetaxel cycles < 6 and ≥ 6 (The ITT Population).



Supplementary figure 3: Kaplan-Meier plots of overall survival for the DP (docetaxel, prednisone and placebo) and the DPL (docetaxel, prednisone and lenalidomide) arm in the subgroups of number of docetaxel cycles ≥ 10 and < 10 (The ITT Population).



Supplementary figure 4: Kaplan-Meier plots of overall survival for patients in the docetaxel prednisone and placebo (DP) and docetaxel prednisone and lenalidomide (DPL) arm. Subgroups of 5-7 cycles docetaxel, 8-10 cycles of docetaxel and > 10 cycles of docetaxel were analyzed. Patients with progressive disease and/or less than ≤ 4 cycles of docetaxel were excluded from the

Supplementary file: protocol summary

The present study contains a posthoc analysis of the Mainsail study, which was a large phase trial that investigated the addition of lenalidomide, an anti-angiogenic agent with immunomodulatory properties, to docetaxel plus prednisone in a randomized double-blind placebo controlled phase 3 clinical trial. The primary analysis of Mainsail was previously published in *Lancet Oncology*¹. Please find a summary of the most important characteristics of the study below that are cited from the original publication.

Selection of patients

- Inclusion criteria
- Men aged 18 years or older at the time of consent;
- Life expectancy of 12 weeks or more;
- Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or lower;
- Haemoglobin concentration more than 9 g/dL;
- Absolute neutrophil count more than 1.5×10^9 cells per L;
- Platelet count more than 100×10^9 cells per L;
- Creatinine clearance level more than 50 mL/min;
- Total bilirubin concentration less than $1.0 \times$ upper limit of normal (ULN);
- Serum aspartate aminotransferase and/or alanine aminotransferase concentrations less than $1.5 \times$ ULN concomitant with alkaline

¹ Petrylak DP, Vogelzang NJ, Budnik N, et al: Docetaxel and prednisone with or without lenalidomide in chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (MAINSAIL): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Oncol* 16:417-25, 2015

phosphatase concentration less than $2.5 \times \text{ULN}$.

Non-taxane-based adjuvant or neoadjuvant treatment completed more than 3 years before randomisation was allowed. Castration was defined as: effective castration as serum testosterone concentrations less than 50 ng/dL. Patients without previous bilateral orchiectomy continued treatment with luteinising hormone-releasing hormone agonists. Otherwise, concurrent anti-androgen therapy was only acceptable per investigator decision, if a 4 week or 6 week delay for anti- androgen washout would not compromise the patient's health and safety.

Exclusion criteria

- A history of clinically significant disease that places subject at an unacceptable risk for study entry
- Prior Therapy with thalidomide, lenalidomide or pomalidomide
- Prior chemotherapy for prostate cancer
- Use of any other experimental drug or therapy within 28 days prior to randomization
- Prior radiation to $\geq 30\%$ of bone marrow or any radiation therapy within 28 days prior to randomization
- Prior use of Strontium-89 at any time or Samarium-153 within 56 days prior to randomization
- Surgery within 28 days prior to randomization
- Concurrent anti-androgen therapy
- Abnormal serum chemistry or hematology laboratory values

- Significant active cardiac disease within the previous 6 months:
- Thrombotic or thromboembolic events within the past 6 months:
- History of peripheral neuropathy of \geq grade 2
- History of severe hypersensitivity reaction to drugs formulated with polysorbate 80
- Paraplegia
- History of Central nervous system (CNS) or brain metastases
- History of malignancies other than prostate cancer within the past 5 years, with the exception of treated basal cell/squamous cell carcinoma of the skin
- Concurrent use of alternative cancer therapies

Schema and treatment plan

Treatment was given in 21 day cycles of intravenous docetaxel (75 mg/m²) on day 1 of each cycle, plus oral prednisone 5 mg twice daily on days 1–21. Patients were pretreated with dexamethasone or corticosteroids, as per docetaxel label. In the lenalidomide group, lenalidomide was given orally at 25 mg/day on days 1–14 of each cycle; placebo was given on days 1–14 in the placebo group.

Rules for dose modification

We permitted dose modifications or discontinuation of study drug for treatment-related toxic effects; patients remained eligible to continue study treatment with the remaining other two drugs. However, complete withdrawal of both drugs resulted in study discontinuation. The lenalidomide dose could be reduced due to adverse events to a minimum of 10 mg/day, with one dose

reduction allowed during any cycle. The docetaxel dose was reduced to 60 mg/m² in case of febrile neutropenia, neutrophil count less than 500 cells per μ L for more than 1 week, severe cumulative cutaneous reactions, or moderate neurosensory symptoms. If the adverse event did not resolve at a docetaxel dose of 60 mg/m², treatment was discontinued. We did not allow re-escalation of lenalidomide or docetaxel after dose reductions. No dose reduction of prednisone was recommended in the protocol.

Measurement of treatment effect

Treatment continued until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, with the exception of progression of bone lesions (non-target lesions) or discontinuation for other reasons. Treatment follow-up occurred every 90 days until death or up to 5 years after discontinuation.

The primary endpoint was overall survival, defined as the time from randomisation to death. Secondary endpoints were progression-free survival (defined as the time from randomisation to disease progression or death); the proportion of patients who achieved an objective response (defined as the proportion of patients with complete response or partial response); and safety. Progression-free survival and the proportion of patients with an objective response were determined by investigators according to RECIST version 1.1 criteria, except bone lesions. Assessments were done with either radiography, CT, and MRI, rather than clinical examination, except when lesions could not be imaged but were assessable by clinical exam; these assessments were done at screening (within 28 days before the first treatment dose, cycle 1 day

1) and then every subsequent third cycle day 1 (ie, every 9 weeks). If no death was reported for a patient before the cutoff date for overall survival analysis, we censored overall survival at the last date at which the patient was known to be alive. For analysis of progression-free survival, we censored patients who had progression or died more than 21 days after study treatment on the date of their last adequate tumour assessment before the last treatment date, plus 21 days. Each tumour assessment was assigned to one of the following categories: complete response, partial response, stable disease, progressive disease, and not evaluable. Patients who received another anti-tumour therapy before progression were censored on the last adequate tumour assessment before receiving the other anti-tumour therapy. Patients who progressed or died immediately after two or more consecutive missed visits for tumour assessment were censored at the date of the last adequate tumour assessment before progression or death. Patients who were still active at data cutoff and who had not progressed were censored on the date of their last adequate tumour assessment. Patients without baseline tumour assessments (or inadequate baseline tumour assessments) were censored on the date of randomisation.

Reasons for early cessation of trial therapy

Treatment continued until disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, with the exception of progression of bone lesions (non-target lesions) or discontinuation for other reasons. Additional reasons for treatment discontinuation included adverse events that, in the judgment of the investigator, could cause severe or permanent harm or could rule out continuation of study drug; disease

progression, except progression attributable to a single new bone lesion; two or more new bone lesions, and for the first post-baseline reassessment only, a confirmatory scan done at least 6 weeks later showing a minimum of two or more additional new lesions; patient withdrawal of consent; patient loss to follow-up; death; protocol violation; patient no longer able to adhere to the protocol (in investigator's opinion); or patient unwilling to comply with the lenalidomide counselling programme.

Safety

We assessed safety by evaluating adverse events (graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0), clinical laboratory data, physical examination, vital signs, concomitant medication and procedures, and electrocardiograms. These data were collected at screening, cycle 1 day 1, cycle 1 day 14, the first day of all subsequent cycles, and at treatment phase discontinuation. Measurements on cycle 1 day 14 were collected for the first 100 patients and any individual participating in the sparse pharmacokinetic sampling substudy, for evaluation during the initial scheduled DMC safety assessment. Additionally, information regarding adverse events and concomitant medications and procedures were also collected during the follow-up phase, at 28 days after last dose. ECGs were done at screening and at treatment phase discontinuation.

Objectives and entire statistical section (including endpoints)

The primary endpoint was overall survival, defined as the time from randomisation to death. Secondary endpoints were progression-free survival

(defined as the time from randomisation to disease progression or death); the proportion of patients who achieved an objective response (defined as the proportion of patients with complete response or partial response); and safety. PSA was an exploratory endpoint, although it was not specified in the protocol.

Assuming that the median overall survival of placebo treatment in this trial would be similar to the published median overall survival (19.2 months) of placebo treatment of the TAX 327 study (docetaxel given every 3 weeks plus prednisone in men with metastatic hormone-resistant prostate cancer), the lenalidomide group had a targeted median overall survival of 25.0 months (30% improvement; targeted hazard ratio [HR] 0.77). This design allowed the demonstration of a significant difference in overall survival at a two-sided 5% significance level with at least 90% or power. We used the O'Brien-Fleming boundary to determine the nominal significance with an overall two-sided 5% significance level. On the basis of these assumptions, we planned to enrol around 1015 chemotherapy-naive patients with metastatic castration-resistant prostate cancer. An interim analysis for overall survival was planned when enrolment was complete and at least 468 events were observed. The final analysis was planned after 624 events and was done by Celgene. In addition to review of efficacy data, an independent data monitoring committee (composed of medical oncologists and a statistician, all of whom were not involved in the study as investigators) also reviewed safety data on a predetermined schedule. We assessed safety data after 100 randomly assigned patients had either completed two treatment cycles or withdrawn from study treatment, and every 6 months after this first review. Furthermore,

an initial safety assessment on day 14 of cycle 1 (for adverse events; physical examination; vital signs; and laboratory results for haematology and serum chemistry) was mandatory for all patients unless the independent data monitoring committee recommended that this assessment was no longer required. Additional safety assessments were to be done by the independent data monitoring committee as appropriate. We did efficacy analyses in the intention-to-treat population, comprising all patients who were randomly assigned. Patients who received at least one dose of study drug were included in the safety analyses.

We analysed overall survival and progression-free survival by the Kaplan-Meier method and log-rank test. We used a Cox proportional hazards regression model with only treatment included in the model to obtain the point estimate for HR and two-sided 95% CIs. All statistical analyses were done with SAS version 9.1 or higher.