Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gwenaelle Gravis, Karim Fizazi, Florence Joly, Stéphane Oudard, Franck Priou, Benjamin Esterni, Igor Latorzeff, Remy Delva, Ivan Krakowski, Brigitte Laguerre, Fréderic Rolland, Christine Théodore, Gael Deplanque, Jean Marc Ferrero, Damien Pouessel, Loïc Mourey, Philippe Beuzeboc, Sylvie Zanetta, Muriel Habibian, Jean François Berdah, Jerome Dauba, Marjorie Baciuchka, Christian Platini, Claude Linassier, Jean Luc Labourey, Jean Pascal Machiels, Claude El Kouri, Alain Ravaud, Etienne Suc, Jean Christophe Eymard, Ali Hasbini, Guilhem Bousquet, Michel Soulie

Summary

Background Early chemotherapy might improve the overall outcomes of patients with metastatic non-castrate (ie, hormone-sensitive) prostate cancer. We investigated the effects of the addition of docetaxel to androgen-deprivation therapy (ADT) for patients with metastatic non-castrate prostate cancer.

Methods In this randomised, open-label, phase 3 study, we enrolled patients in 29 centres in France and one in Belgium. Eligible patients were older than 18 years and had histologically confirmed adenocarcinoma of the prostate and radiologically proven metastatic disease; a Karnofsky score of at least 70%; a life expectancy of at least 3 months; and adequate hepatic, haematological, and renal function. They were randomly assigned to receive to ADT (orchiectomy or luteinising hormone-releasing hormone agonists, alone or combined with non-steroidal antiandrogens) alone or in combination with docetaxel (75 mg/m² intravenously on the first day of each 21-day cycle; up to nine cycles). Patients were randomised in a 1:1 ratio, with dynamic minimisation to minimise imbalances in previous systemic treatment with ADT, chemotherapy for local disease or isolated rising concentration of serum prostate-specific antigen, and Glass risk groups. Patients, physicians, and data analysts were not masked to treatment allocation. The primary endpoint was overall survival. Efficacy analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00104715.

Findings Between Oct 18, 2004, and Dec 31, 2008, 192 patients were randomly allocated to receive ADT plus docetaxel and 193 to receive ADT alone. Median follow-up was 50 months (IQR 39–63). Median overall survival was 58·9 months (95% CI 50·8–69·1) in the group given ADT plus docetaxel and 54·2 months (42·2–not reached) in that given ADT alone (hazard ratio 1·01, 95% CI 0·75–1·36). 72 serious adverse events were reported in the group given ADT plus docetaxel, of which the most frequent were neutropenia (40 [21%]), febrile neutropenia (six [3%]), abnormal liver function tests (three [2%]), and neutropenia with infection (two [1%]). Four treatment-related deaths occurred in the ADT plus docetaxel group (two of which were neutropenia-related), after which the data monitoring committee recommended treatment with granulocyte colony-stimulating factor. After this recommendation, no further treatment-related deaths occurred. No serious adverse events were reported in the ADT alone group.

Interpretation Docetaxel should not be used as part of first-line treatment for patients with non-castrate metastatic prostate cancer.

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Medical Oncology (G Gravis MD) **and Biostatistics** (B Esterni MSc), **Institut Paoli-Calmettes, Marseille, France; Department of Cancer Medicine, Institut Gustave Roussy, University of Paris Sud, Villejuif, France** (Prof K Fizazi MD); **Medical Oncology, Centre François Baclesse, Centre Hospitalier Universitaire Côte de Nacre, Caen, France** (Prof F Joly MD); **Medical Oncology Department, Georges Pompidou Hospital and Rene Descartes University, Paris, France** (Prof S Oudard MD); **Medical Oncology, Centre Hospitalier Les Oudairies, La Roche-sur-Yon, France** (F Priou MD); **Radiotherapy Department, Clinique Pasteur, Toulouse, France** (I Latorzeff MD); **Department of Medical Oncology, Centre Paul Papin, Angers, France** (R Delva MD); **Medical Oncology, Centre Alexis Vautrin, Vandoeuvre-lès-Nancy, France** (Prof I Krakowski MD); **Medical Oncology, Centre Eugène Marquis, Rennes, France** (B Laguerre MD); **Medical Oncology, Centre René Gauducheau, Saint-Herblain, France** (F Rolland MD); **Medical Oncology, Hôpital Foch, Suresnes, France** (C Théodore MD); **Medical Oncology, Groupe Hospitalier Saint Joseph, Paris, France** (G Deplanque MD); **Medical Oncology, Centre Antoine Lacassagne, Nice, France** (Prof J M Ferrero MD); **Medical Oncology, Centre Val d'Aurelle-Paul Lamarque, Montpellier, France**

Introduction

Worldwide, prostate cancer is the second most common malignancy[1] and is the third most common cause of cancer death in men in developed countries.[2] Metastases are rare at the time of diagnosis—at least in developed countries[3]—but can eventually develop after failure of local treatment. Bilateral orchiectomy (medical castration) is recommended for initial treatment of non-castrate (ie, hormone-sensitive) metastatic prostate cancer.[4,5] Median duration of sensitivity to androgen-deprivation therapy (ADT) is usually 24–36 months;[6] before new active drugs were introduced, median survival was about 30 months (95% CI 12–53).[7] However, the outcome of this treatment varies widely. A set of prognostic groups was developed that separated patients on the basis of appendicular versus axial disease, an Eastern Cooperative Oncology Group performance status of 0 versus 1–3, concentration of prostate-specific antigen (PSA) of less than 65 ng/mL versus 65 ng/mL or more, and a Gleason score less than 8 versus 8 or more.[8] With these criteria, three groups were identified: good (42% of patients survive to 5 years), intermediate (21%), and poor (9%) prognosis.[8]

Metastatic prostate cancer eventually becomes resistant to castration. Until 2004, docetaxel with prednisone was the only treatment that could improve survival.[9,10] The benefit of these drugs in castration-resistant prostate cancer suggested that early chemotherapy might improve

(D Pouessel MD); **Medical Oncology, Institut Claudius Régaud, Toulouse, France** (L Mourey MD); **Medical Oncology, Institut Curie, Paris,France** (P Beuzeboc MD); **Medical Oncology, Centre Georges François Leclerc, Dijon, France** (S Zanetta MD); **R&D UNICANCER, Paris, France** (M Habibian); **Medical Oncology, Clinique Sainte Marguerite, Hyeres, France** (J F Berdah MD); **Medical Oncology, Hôpital Layné, Mont-de-Marsan, France** (J Dauba MD); **Medical Oncology, Centre Hospitalier La Timone, Marseille, France** (M Baciuchka MD); **Medical Oncology, Centre Régional Hospitalier Metz-Thionville, Thionville, France** (C Platini MD); **Medical Oncology, Hôpital Bretonneau, Tours, France** (Prof C Linassier MD); **Medical Oncology, Centre Hospitalier Dupuytren, Limoges, France** (J L Labourey MD); **Medical Oncology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium** (Prof J P Machiels MD); **Medical Oncology, Centre Catherine de Sienne, Nantes, France** (C El Kouri MD); **Medical Oncology, Hôpital Saint-André, Bordeaux, France** (Prof A Ravaud MD); **Medical Oncology, Clinique Saint-Jean Languedoc, Toulouse, France** (E Suc MD); **Medical Oncology, Institut Jean Godinot, Reims, France** (J C Eymard MD); **Medical Oncology, Clinique Armoricaine de Radiologie, Saint-Brieuc, France** (A Hasbini MD); **Medical Oncology, Hôpital Saint-Louis, Paris, France** (G Bousquet MD); **and Urology Department, Centre Hospitalier Universitaire Rangueil, Toulouse, France** (Prof M Soulie MD)

Correspondence to:
Dr Gwenaelle Gravis, Medical Oncology, Institut Paoli-Calmettes, Centre de Recherche en Cancérologie de Marseille, UMR891 Inserm, 13009 Marseille, France
gravisg@ipc.unicancer.fr

For the **trial protocol** see http://www.unicancer.fr/sites/default/files/UNICANCER_Protocole_GETUG_15.pdf

the overall outcome of patients with metastatic non-castrate prostate cancer. Thus, we aimed to assess the efficacy and safety of docetaxel combined with ADT versus ADT alone in patients with metastatic non-castrate prostate cancer.

Methods

Participants

In this randomised, open-label, phase 3 trial, we enrolled participants from 29 centres in France and one in Belgium. Individuals aged more than 18 years were eligible if they had histologically confirmed adenocarcinoma of the prostate and radiologically proven metastatic disease; a Karnofsky score of at least 70%; a life expectancy of at least 3 months; and adequate hepatic, haematological, and renal function. Patients who had received previous chemotherapy for metastatic disease were excluded, but ADT for patients with metastatic disease could have been initiated no more than 2 months before enrolment. In the neoadjuvant and adjuvant settings or in the context of isolated PSA increase, previous chemotherapy or ADT, or both, were allowed, with the condition that the treatment had been discontinued at least 12 months before inclusion in the study and no metastases or PSA increase had been documented during this period. Radiotherapy for metastatic disease was to be completed at least 4 weeks before enrolment.

Patients were excluded from study entry when they had severe cardiac disease, had had surgical castration before metastatic disease occurred, had evidence of brain metastasis, had peripheral neuropathy (at least grade 2), a history of another cancer in the past 5 years (except basal-cell or squamous-cell skin cancer), or another serious condition that could jeopardise their participation.

The protocol was reviewed by the internal review boards of all participating institutions and the study was approved by a central national ethics committee. The study was done in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent.

Randomisation and masking

Randomisation was done by a clinical research organisation and was centralised nationally. Patients were randomly allocated in a 1:1 ratio to receive ADT plus docetaxel or ADT alone. Dynamic minimisation was used to minimise the imbalance of three criteria: previous systemic treatment with ADT; chemotherapy for local disease or isolated rising PSA; and Glass risk groups.[8] Patients, physicians, and data analysts were not masked to treatment allocation.

Procedures

All patients received ADT, which consisted of orchiectomy or luteinising hormone-releasing hormone agonists, alone or combined with non-steroidal antiandrogens. ADT was given continuously until unacceptable toxic effects or discontinuation on patients' request. In the group given ADT plus docetaxel, patients received 75 mg/m² intravenous docetaxel in a 250 cm³ 5% glucose solution in the course of 1 h on the first day of each 21-day cycle. Treatment with docetaxel continued for up to nine cycles on the basis of the median exposure reported in the TAX 327 trial,[9] or was discontinued prematurely in the case of progression, unacceptable toxic effects, or patients' request. Premedication with a corticosteroid (8 mg dexamethasone or equivalent) was given orally in the evening before the infusion of docetaxel, on the day of docetaxel infusion, and on the next day.

If predefined toxic effects occurred (haematological or non-haematological effects; gastrointestinal, skin, and liver toxic effects; peripheral neuropathy; or docetaxel-specific adverse events), docetaxel could be delayed until recovery or the dose could be reduced by up to 25%. Bisphosphonates were allowed with first-line treatment.

We assessed clinical history, weight, and Karnofsky performance status, and did a physical examination before treatment began. We did a CT scan, a bone scan, electrocardiography, and blood tests (including measurement of serum PSA) within 30 days before initiation of treatment. We repeated physical examinations and blood tests every 3 weeks during treatment in the group given ADT plus docetaxel and every 3 months in the group given ADT alone. We did imaging studies every 3 months; radiological response was to be confirmed within 4 weeks. After 42 months, we did clinical, laboratory, and radiological examinations every 6 months.

The primary endpoint was overall survival (ie, time between randomisation and death from any cause). Secondary endpoints were time to clinical progression or death (clinical progression-free survival; cPFS) and time to PSA progression, clinical progression, or death (biochemical progression-free survival; bPFS).

We defined biochemical progression with the PSA Working Group definition:[11] a previous confirmed PSA decrease of at least 50% and an increase of at least 50% above the nadir, with a minimum increase of 5 ng/mL. For patients without a previous PSA decrease of 50%, progression was defined as a PSA increase of at least 25% above the nadir and of at least 5 ng/mL. A confirmatory PSA test was mandatory in all cases. In patients with measurable lesions, we defined clinical progression as the progression of pre-existing lesions with Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0)[12] or the occurrence of (new) bone lesions, whichever happened first. In patients with only bone lesions, progression was defined as one or more new bone lesions on bone scan or occurrence of a new soft-tissue lesion, whichever happened first. Death was judged as an event; causes of deaths were reported by investigators rather than by central review.

We assessed adverse events with the Common Toxicity Criteria of the National Cancer Institute (version 3). Quality of life was assessed with the self-administered

European Organisation for Research and Treatment of Cancer quality-of-life questionnaire C30. Patients completed the questionnaire at initiation, 3 months, and 6 months, and then subsequently twice a year.

Statistical analysis

The planned sample of 378 patients provided 80% power to detect a hazard ratio (HR) of 0·62 for death in the group receiving ADT plus docetaxel as compared with that receiving ADT alone. We calculated this sample size with the assumption that 65% of the group given ADT plus docetaxel and 50% of the group given ADT alone would survive to 36 months,[7,8,13] with a two-sided α of 0·05 and a fixed 36-month follow-up period to record the 146 necessary events. Initially, the study was planned with only 36 months of follow-up for all patients. To reach the number of necessary events, the sponsor decided to follow up all enrolled patients until one cutoff date, namely July 31, 2011. Patients with no event at the last visit or on July 31, 2011, were censored.

We did the efficacy analyses by intention to treat. Safety analyses were based on the population exposed to the assigned treatment. We did post-hoc subgroup analyses to assess whether specific baseline characteristics affected overall survival and bPFS. We estimated distributions of time-to-event variables and associated 95% CIs with the Kaplan-Meier product-limit method. The log-rank test was the primary analysis for comparison of treatment groups. We estimated adjusted and unadjusted treatment effects with the Cox proportional-hazards model. Because PSA progression is a time-dependent covariate, we used a 7-month landmark analysis to investigate its effect on overall survival. We chose to do a landmark analysis with bPFS because cPFS is difficult to assess in metastatic prostate cancer and bPFS was considered to be more specific than is cPFS. We chose 7 months to compare our results with those of the landmark analysis of Hussain and colleagues.[14]

We estimated follow-up with the reverse censoring method and time to subsequent treatments with standard descriptive median on the restricted population who received at least one treatment. We tested the proportional hazard assumption with the Grambsch and Therneau method.[15] Other statistical inferences were assessed with the χ^2 statistic. All statistical analyses were done with R (version 2.15.1).

This trial is registered with ClinicalTrials.gov, number NCT00104715.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Raw data was the property of UNICANCER, and all authors could access the data by request to UNICANCER and the corresponding author. UNICANCER and GG had final responsibility for the decision to submit for publication.

Results

Between Oct 18, 2004, and Dec 31, 2008, we enrolled 385 patients (figure 1). Most patients had metastases at the time of diagnosis of prostate cancer; the remaining

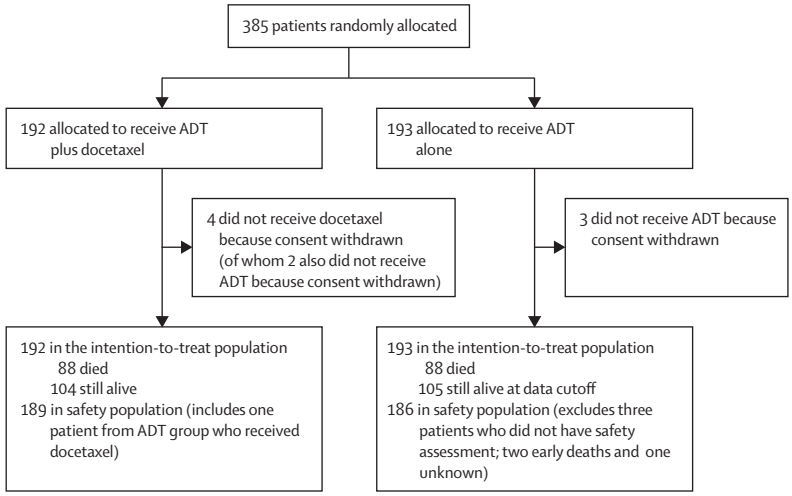

Figure 1: **Trial profile and patient disposition at data cutoff**
ADT=androgen-deprivation therapy.

	ADT plus docetaxel (n=192)	ADT alone (n=193)
Age (years)	63 (57–68)	64 (58–70)
Initial Gleason score*		
2–6	18 (10%)	14 (7%)
7	66 (35%)	64 (34%)
8–10	103 (55%)	113 (59%)
Metastatic after treatment for local disease	62 (32%)	46 (24%)
Metastatic at diagnosis	128 (67%)	144 (75%)
Time from diagnosis of prostate cancer to randomisation (months)	2·50 (1·55–10·91)	2·07 (1·36–4·97)
Metastatic sites		
Bone	155 (81%)	156 (81%)
Nodes	100 (52%)	108 (56%)
Lung	22 (11%)	22 (11%)
Liver	9 (5%)	3 (2%)
Karnofsky score	100% (90–100)	100% (80–100)
Serum concentration of prostate-specific antigen (ng/mL)	26·7 (5·0–106·2)	25·8 (5·0–126·9)
Glass prognostic group[8]		
Good	95 (49%)	96 (50%)
Intermediate	54 (28%)	57 (30%)
Poor	43 (22%)	40 (21%)
EORTC QLQ–C30 global scores	67·4 (20·2)	65·4 (21·9)
Initiation of ADT		
15–60 days before enrolment	101 (53%)	91 (47%)
Within 15 days of enrolment	91 (47%)	102 (53%)

Data are median (IQR), n (%), or mean (SD). ADT=androgen-deprivation therapy. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer quality-of-life questionnaire C30. *Data missing for five patients in group given ADT plus docetaxel and two patients in group given ADT alone.

Table 1: **Baseline characteristics**

patients developed metastases after local treatment. Metastatic sites were mainly bone, nodes, and lungs (table 1). Metastases in extrapelvic nodes were reported in only 55 (14%) patients. No patients were lost to follow-up.

See Online for appendix

	Androgen-deprivation therapy plus docetaxel (n=192)	Androgen-deprivation therapy alone (n=193)
Docetaxel	54 (28%)	120 (62%)
Cabazitaxel	3 (2%)	2 (1%)
Included in a randomised study		
Abiraterone *vs* placebo	19 (10%)	21 (11%)
Enzalutamide *vs* placebo	9 (5%)	7 (4%)
Orteronel *vs* placebo	2 (1%)	1 (<1%)
Other experimental treatment*	13 (7%)	22 (11%)
Anthracycline	23 (12%)	34 (18%)
Etoposide	24 (13%)	26 (13%)
Platinum-based chemotherapy	21 (11%)	22 (11%)
Cyclophosphamide	8 (4%)	9 (5%)
Vinorelbine	9 (5%)	11 (6%)
Paclitaxel	4 (2%)	5 (3%)
Fluoropyrimidine	2 (1%)	1 (<1%)

Data are n (%). Some patients received more than one additional treatment. *Patients received efavirenz, BIBF 1120, enzastaurine, sagopilone, DTS-201, CNTO 328, or masitinib; or were included in randomised studies testing ipilimumab, dasatinib, zibotentan, sunitinib, vandetanib, or aflibercept against placebo.

Table 2: **Treatments at progression**

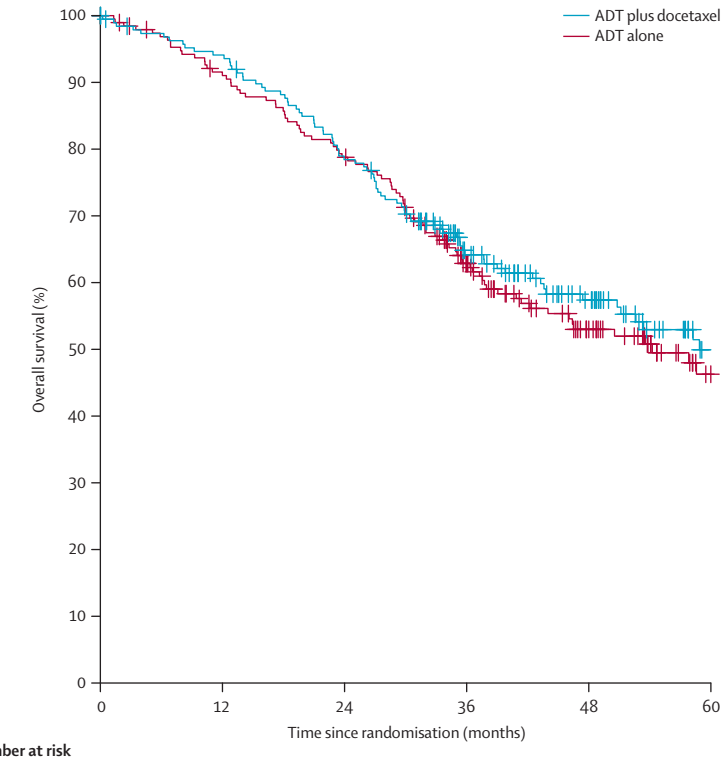

Figure 2: **Kaplan-Meier curves for overall survival by treatment group**
Crosses indicate censoring. ADT=androgen-deprivation therapy.

One patient in the group assigned to receive ADT alone received docetaxel and was included in the group given ADT plus docetaxel for the safety analyses (figure 1). ADT was started between 15 days and 2 months before randomisation in roughly half the patients (table 1). In the group given ADT plus docetaxel, castration was obtained with luteinising hormone-releasing hormone agonists alone in 67 patients (35%) and with combined blockade in 123 patients (64%; two patients did not receive ADT because consent withdrawn). In the group given ADT alone, luteinising hormone-releasing hormone alone was used in 59 patients (31%) and combined blockade in 131 patients (68%; three patients did not receive ADT because consent withdrawn).

The median number of docetaxel cycles was eight (range zero to nine); 93 patients (48%) received the nine planned cycles. Doses were reduced in 21 (11%) of the 189 patients who received docetaxel. Of the 99 patients who discontinued docetaxel, 39 did so due to toxic effects, six due to disease progression, two due to protocol violations, and 52 for other reasons.

120 (62%) of the 193 patients allocated to receive ADT alone subsequently received docetaxel at the time of progression of castration-resistant prostate cancer and 54 (28%) of the 192 patients allocated to receive ADT plus docetaxel were rechallenged with docetaxel at the time of progression to castration resistance. The median length of time from randomisation to subsequent chemotherapy was 16 months (IQR 10–24) in the group given ADT alone versus 26 months (18–36) in the group given ADT plus docetaxel.

After progression, some patients received other treatments that could have affected survival (table 2). First-line bisphosphonates were given to 34 patients (18%) in the group given ADT plus docetaxel and 25 (13%) in that given ADT alone (p=0·25).

Median follow-up was 50 months (IQR 39–63). At the cutoff date (July 31, 2011), 176 patients—88 (46%) in each group—had died (figure 1). Causes of death were disease progression (68 [77%] in the group given ADT plus docetaxel; 75 [85%] in the group given ADT alone), treatment-related toxic effects (two [2%; none), other cancers (five [6%]; none), other reasons (five [6%]; six [7%]), and unknown reasons (eight [9%]; seven [8%]). Subsequent UNICANCER review deemed that four deaths (5%) in the group given ADT plus docetaxel were treatment-related; one death had previously been thought to be due to progressive disease, but no information was available for the other additional treatment-related death.

Median overall survival was 58·9 months (95% CI 50·8–69·1) in the group given ADT plus docetaxel and 54·2 months (42·2–not reached) in the group given ADT alone (HR 1·01, 95% CI 0·75–1·36; p=0·955; figure 2). 3-year overall survival was 64·2% (95% CI 57·5–71·6) in the group given ADT plus docetaxel and 62·9% (56·3–70·2) in the group given ADT alone.

Median bPFS was significantly longer in the group given ADT plus docetaxel (22·9 months, 95% CI 19·6–28·4) than in the group given ADT alone (12·9 months, 11·9–17·7; HR 0·72, 0·57–0·91; p=0·005; figure 3). Similarly, median cPFS was significantly longer in the group given ADT plus docetaxel (23·5 months, 20·5–31·9) than in the group given ADT alone (15·4 months, 12·5–19·8; HR 0.75, 0·59–0·94; p=0·015; figure 3).

Median overall survival and bPFS in subgroups did not differ significantly in the two treatment groups (figures 4, 5). When we pooled data from all patients, we noted that median overall survival was significantly longer in the good-prognosis subgroup (69·1 months, 95% CI 60·9–not reached) than in intermediate-prognosis (46·5 months, 37·7–not reached) and poor-prognosis subgroups (36·6 months, 28·5–58·9; p=0·001 for comparison between all three subgroups), with no difference between intermediate-prognosis and poor-prognosis groups.

Median time to subsequent treatment (hormone therapy or chemotherapy) was 20·0 months (IQR 14·6–27·1) in the group given ADT plus docetaxel and 15·4 months (9·2–21·4) in the group given ADT alone. More patients in the group given ADT alone than in that given ADT plus docetaxel had an increase in serum PSA concentration of more than 25% from baseline at 6 months (16 [10%] of 162 for whom data were available *vs* two [1%] of 164; p=0·0015). Falls in serum PSA concentration of more than 50% occurred more frequently in the group given ADT plus docetaxel than in that given ADT alone at 3 months (156 [91%] of 172 *vs* 148 [80%] of 184; p=0·0096) and at 6 months (161 [94%] of 172 *vs* 157 [85%] of 184; p=0·0185).

Biochemical progression was associated with decreased overall survival, as shown by the landmark analysis at 7 months (HR 4·26, 95% CI 3·01–6·02; p<0·0001; appendix).

The proportional-hazards model showed that the HR for death was stable with time in both groups (constant effect of treatment allocation with regards to overall survival). By contrast, the HR for biochemical or clinical progression was not constant (p=0·001), with a significant decrease in the beneficial effects of chemotherapy with time (appendix).[15] Because of the non-proportional hazards, we used average HRs as a sensitivity analysis to estimate the treatment effect and provided similar results for bPFS (average HR 0·66 [95% CI 0·52–0·84]) and cPFS (0·69 [0·54–0·89]).[16]

In the group given ADT plus docetaxel, 39 (21%) of 189 patients in the safety population stopped treatment because of toxic effects. Roughly a third of patients in this group experienced neutropenia of grade 3–5 and some had febrile neutropenia of grade 3–5 (table 3). After accrual of 215 patients (108 to group given ADT plus docetaxel; 107 to group given ADT alone), four treatment-related deaths had been reported in the group given ADT

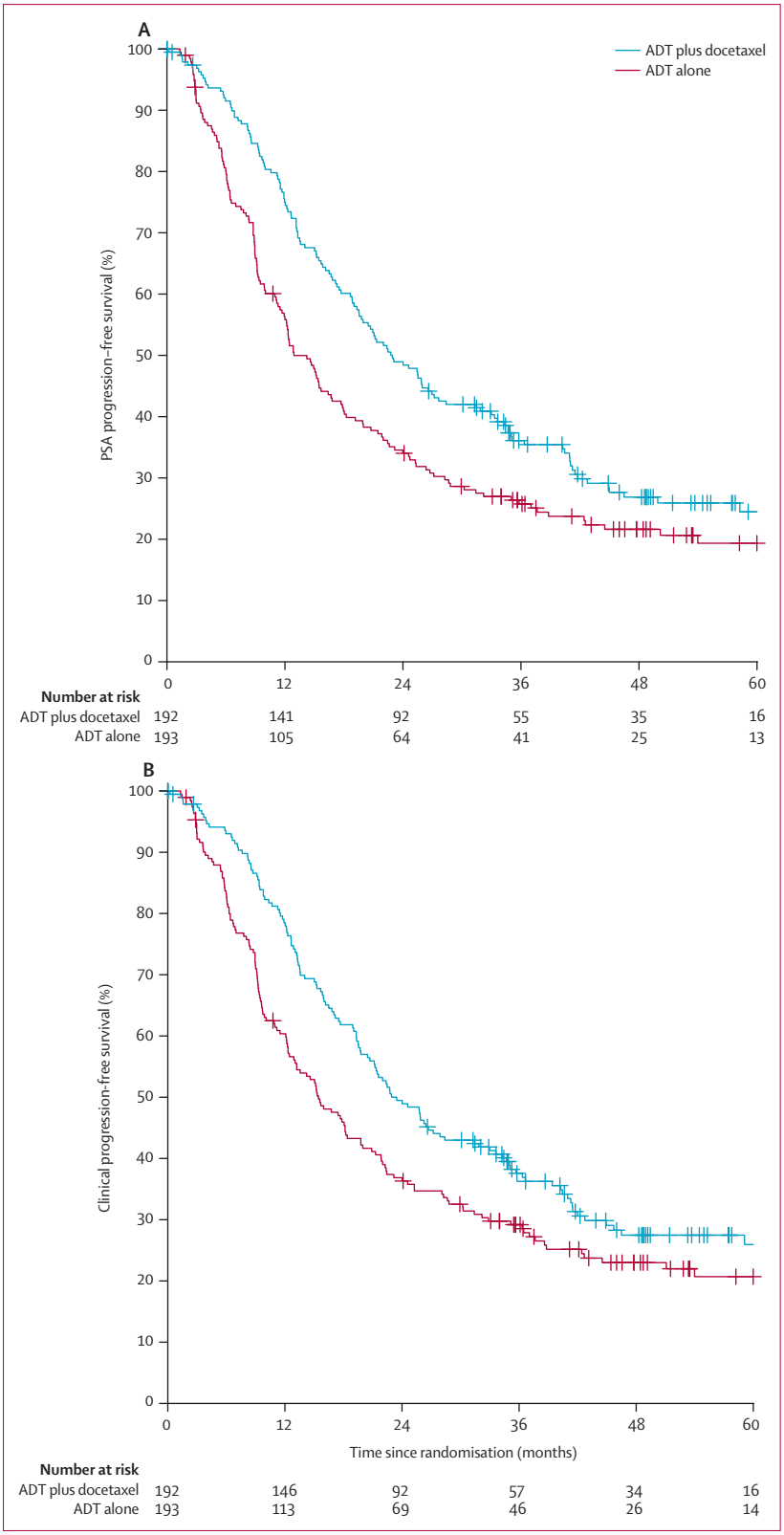

***Figure 3*: Kaplan-Meier curves for PSA progression-free survival (A) and clinical progression-free survival (B) by treatment group**
Crosses indicate censoring. PSA=prostate-specific antigen. ADT=androgen-deprivation therapy.

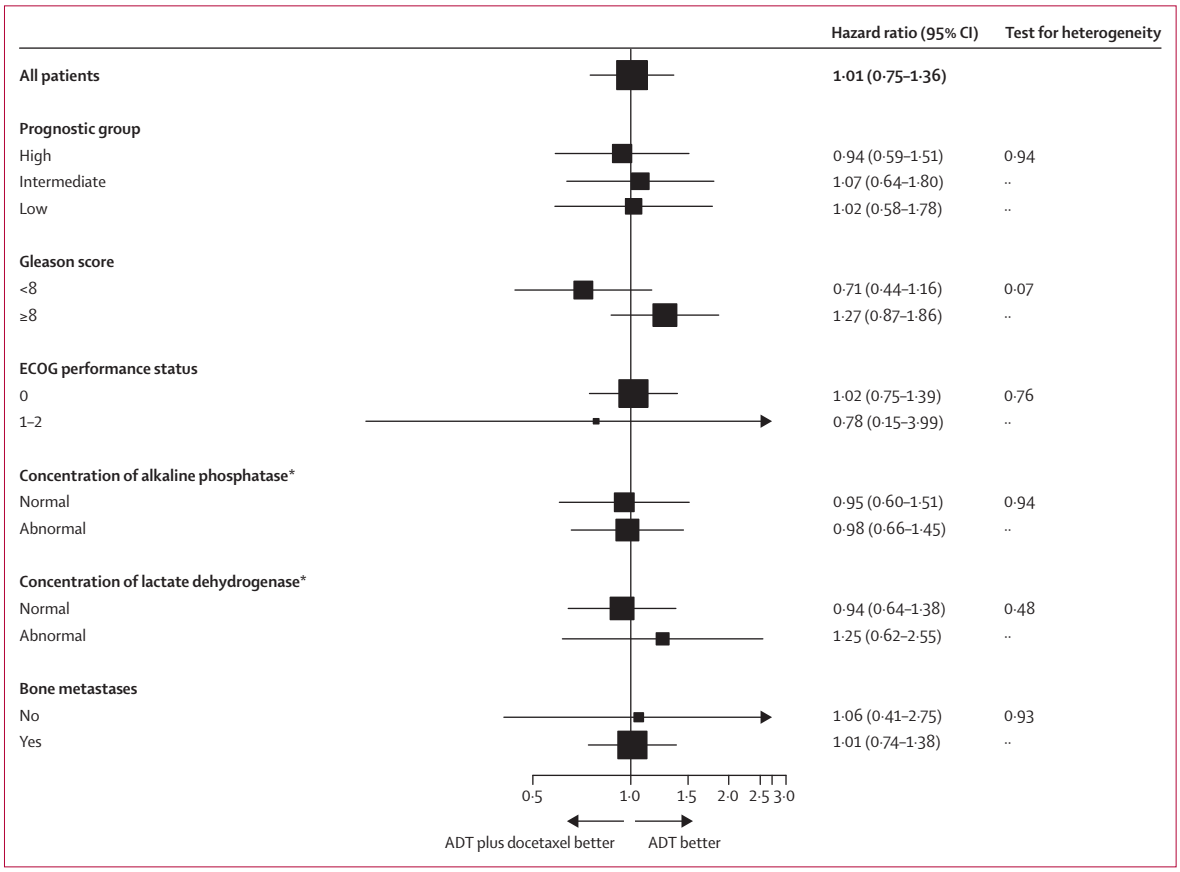

Figure 4: **Forest plot of median overall survival according to baseline characteristics**
ECOG=Eastern Cooperative Oncology Group. ADT=androgen-deprivation therapy. *Abnormal concentrations were defined as those higher than the upper limit of normal and below the lower limit of normal in the laboratories.

plus docetaxel: one due to febrile neutropenia, one neutropenia with infection, one multiorgan failure, and one pulmonary embolism. The independent data monitoring committee subsequently recommended granulocyte colony-stimulating factor (5 μg/kg/day subcutaneously once a day) from day 5 to day 10 after each docetaxel treatment. After this amendment, the number of patients with grade 3–4 neutropenia fell from 51 (41%) of 123 to ten (15%) of 66 patients, and the number with grade 3–4 febrile neutropenia decreased from ten (8%) of 123 to four (6%) of 66. No subsequent deaths due to toxic effects were recorded.

72 serious adverse events (defined as events that result in death; are life-threatening; result in admission or extension of hospital stay; cause permanent disability or serious temporary incapacity; cause a congenital anomaly, a fetal malformation, or a miscarriage; or is medically significant) were reported in the group given ADT plus docetaxel, of which the most common (ie, occurring in at least 1% of patients) were neutropenia (40 patients [21%]), febrile neutropenia (six [3%]), abnormal liver function tests (three [2%]), and neutropenia with infection (two [1%]). The most common grade 3–5 adverse events in the ADT and docetaxel group were neutropenia, febrile neutropenia, erectile dysfunction, and fatigue (table 3). No severe adverse events were reported in the ADT alone group. Anaemia, hot flushes, decreased libido, and erectile dysfunction were the most frequently reported adverse events in this group, although few were of grades 3–5 (table 3).

At baseline, mean quality-of-life scores were similar in the two groups (ADT plus docetaxel: 67·41 [SD 20·2]; ADT alone 65·38 [21·9]; p=0·405; appendix). Mean scores were significantly lower in the group given ADT plus docetaxel than in that given ADT alone during the treatment phase (month 3: 63·95 [18·5] *vs* 70·96 [20·7], p=0·005; month 6: 61·84 [20·2] *vs* 70·92 [16·8], p=0·001; appendix). However, no differences in mean global and functional scores were recorded between the two groups at 12 months (67·62 [18·4] *vs* 66·36 [20·2]; p=0·696), except for appetite loss (2·31 [8·5] vs 9·96 [22·8]; p=0·005) and constipation (10·95 [21·0] *vs* 21·69 [31·0]; p=0·012), which were more frequent in the group given ADT plus docetaxel than in that given ADT alone (appendix).

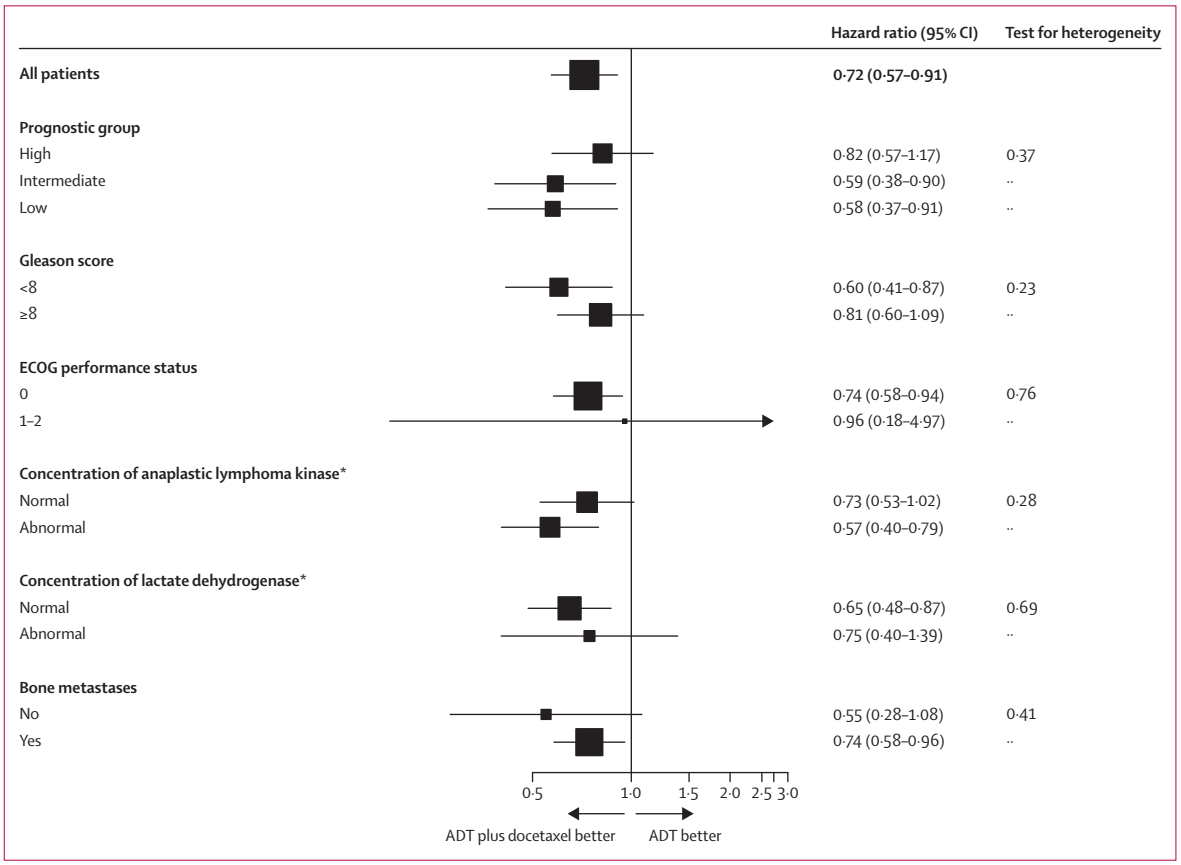

Figure 5: **Forest plot of median biochemical progression-free survival according to baseline characteristics**
ECOG=Eastern Cooperative Oncology Group. ADT=androgen-deprivation therapy. *Abnormal concentrations were defined as those higher than the upper limit of normal and below the lower limit of normal in the laboratories.

Discussion

We have shown that the combination of ADT plus docetaxel in patients with metastatic non-castrate prostate cancer did not significantly increase overall survival compared with ADT alone.

Overall survival is deemed to be the best endpoint to assess the outcome of anticancer treatments—especially in prostate cancer—because response and progression of bone metastases is often difficult to measure and the value of PSA as a surrogate endpoint is controversial. In our study, the absence of a difference between groups probably cannot be explained by insufficient follow-up duration, because we did not record even a slight beneficial effect of chemotherapy. However, overall survival was affected by crossover treatments: in our study, almost two-thirds of patients assigned to receive ADT alone were given docetaxel at the time of castration-resistant prostate cancer progression, but just over a quarter of those assigned to receive ADT plus docetaxel received additional docetaxel-based chemotherapy, which potentially confounded detection of a treatment-related survival benefit.

We did show improvements with ADT plus docetaxel in all efficacy secondary endpoints, such as PSA increase, bPFS, and cPFS. The discrepancies between bPFS and time to subsequent treatment were due to the different estimation methods. Because we obtained relevant information only if a new treatment was reported, we estimated the median time to new treatment only in patients who received a new treatment. We estimated other median survival measures (bPFS, cPFS) with the Kaplan-Meier method and censored times for patients without events. Median bPFS and cPFS in populations restricted to individuals with a documented new treatment were lower than in the whole population (18 months and 19 months in the group given ADT plus docetaxel; 11 months and 12 months in the group given ADT alone).

The secondary endpoints are clinically relevant. Early PSA progression (an increase of ≥25%) within the first 6 months of treatment correlates with overall survival in both non-castrate and castration-resistant prostate cancer.[17] The analysis[18] of the TAX 327 study of patients with metastatic castration-resistant prostate cancer showed that PSA response (ie, at least 50% reduction in serum PSA from baseline that was maintained for at least 3 weeks) was associated with longer survival. Final results of the S9346 study[19] showed that median overall survival was 3·6 years

	Androgen-deprivation therapy plus docetaxel (n=189)			Androgen-deprivation therapy alone (n=186)		
	Grade 1–5	Grade 3–4	Grade 5	Grade 1–5	Grade 3–5	Grade 5
Neutropenia	94 (50%)	61 (32%)	0	5 (3%)	0	0
Febrile neutropenia	15 (8%)	14 (7%)	1 (<1%)	0	0	0
Infections with neutropenia	5 (3%)	4 (2%)	1 (<1%)	0	0	0
Anaemia	136 (72%)	4 (2%)	0	41 (22%)	2 (1%)	0
Thrombocytopenia	20 (11%)	1 (<1%)	0	9 (5%)	0	0
Fatigue	140 (74%)	13 (7%)	0	37 (20%)	2 (1%)	0
Nausea	55 (29%)	0	0	4 (2%)	0	0
Vomiting	16 (8%)	0 (0%)	0	0	0	0
Diarrhoea	58 (31%)	1 (<1%)	0	4 (2%)	0	0
Constipation	42 (22%)	0	0	9 (5%)	0	0
Alopecia	102 (54%)	5 (3%)	0	1 (<1%)	0	0
Sensory neuropathy	54 (29%)	3 (2%)	0	7 (4%)	0	0
Nail changes	74 (39%)	5 (3%)	0	0	0	0
Peripheral oedema	55 (29%)	2 (1%)	0	10	0	0
Dyspnoea	36 (19%)	4 (2%)	0	6 (3%)	0	0
Stomatitis	15 (8%)	1 (<1%)	0	0	0	0
Mucositis	40 (21%)	1 (<1%)	0	0	0	0
Hot flushes	70 (37%)	8 (4%)	0	118 (63%)	3 (2%)	0
Erectile dysfunction	21 (11%)	16 (8%)	0	23 (12%)	14 (8%)	0
Decreased libido	21 (11%)	12 (6%)	0	28 (15%)	9 (5%)	0
Gynaecomastia	8 (4%)	0 (0%)	0	10 (5%)	1 (<1%)	0
Increased concentrations of alanine aminotransferase	43 (23%)	3 (2%)	0	22 (12%)	1 (<1%)	0
Increased concentrations of aspartate aminotransferase	38 (20%)	3 (2%)	0	17 (9%)	1 (<1%)	0
Other	131 (69%)	13 (7%)	2 (1%)	56 (30%)	1 (<1%)	0

Table 3: **Toxic effects reported in the first 6 months of treatment**

for the international population of patients with metastatic non-castrate prostate cancer but longer than 5 years in patients who had achieved a serum PSA concentration of 4·0 ng/mL or less after 6 or 7 months of treatment.

Notably, we showed that the progression-hazards model was not proportional (whether biochemical or clinical), with a decrease in the beneficial effect of chemotherapy with time; therefore, docetaxel efficacy diminishes before progression occurs. This finding could partly explain the absence of a difference in overall survival between the two groups, despite the short-term efficacy of chemotherapy in terms of biological variables.

Median overall survival in our study was longer than that previously reported in patients with metastatic non-castrate prostate cancer treated with ADT,[19,20] which is another possible explanation for the absence of survival difference between the two groups. Our initial hypothesis was that we would record a median survival of 3 years in the group given ADT alone on the basis of previous reports, but median survival in our cohort was longer than expected (54·2 months [4·5 years]). Our patients might have been diagnosed earlier in their history of metastatic disease than have others, because PSA measurement and improved imaging techniques are now frequently used. In a previous study,[20] survival was different between cohorts included at different periods; median survival was 33 months in S8894 (patients included from 1989 to 1994) and 49 months in S9346 (patients included from 1995 to 2009). Additionally, an increased prevalence of widespread disease and bone pain and substantially higher PSA concentrations were recorded in early trials.[20]

Differences in survival between our study and others persist in the subgroup analysis. In the study by Glass and colleagues,[8] median overall survival was 54 months in the good-prognosis group, 30 months in the intermediate-prognosis group, and 21 months in the poor-prognosis group—ie, all shorter than in our trial. Longer survival in our study could be due to improved treatment in metastatic castration-resistant prostate cancer or stage migration in patients with metastatic disease. However, most participants in our trial had bone or visceral metastases (few had isolated node involvement).

Therefore, several possible reasons exist for the absence of a difference in overall survival between the two groups in our study. First, docetaxel does not confer benefits in metastatic non-castrate prostate cancer, or alternatively docetaxel has a decreasing effect on progression-free survival that does not confer advantages in terms of overall survival. Second, we might not have calculated an appropriate sample size, because survival duration might have been underestimated for the group given ADT alone and difference in the group given ADT plus docetaxel overestimated. Third, crossover to docetaxel at the time of progression might have had an effect.

Very few studies and no phase 3 trials have assessed the combination of docetaxel-based chemotherapy and ADT in metastatic non-castrate prostate cancer (panel). Millikan and colleagues[21] included 286 patients and compared ketoconazole and doxorubicin alternating with vinblastine and estramustine given with ADT versus standard ADT. They recorded no significant differences in time to progression of castration-resistant prostate cancer and in median survival between the two groups.[21] A study by Wang and coworkers[22] compared the combination of mitoxantrone and ADT with ADT alone in 93 patients with locally advanced (n=38) or metastatic (n=55) prostate cancer. Overall survival and responses were significantly improved in patients with locally advanced disease given mitoxantrone, but patients with metastatic disease did not benefit.

Some studies have investigated the addition of chemotherapy to ADT in early-stage prostate cancers. The preliminary results of the GETUG 12 phase 3 study,[23] which compared ADT alone and ADT plus docetaxel and estramustine in high-risk prostate cancers treated locally mainly by radiotherapy, showed that PSA response was significantly higher in the group given chemotherapy than in that given ADT alone, but long-term data are not available yet. The results of the SWOG S9921 study,[24] which compared ADT alone or in combination with mitoxantrone as adjuvant therapy in high-risk men who

Panel: Research in context

Systematic review

We searched Medline and PubMed for reports published in English or French between Jan 1, 1994, and June 1, 2004, with the search terms "prostate cancer", "metastatic prostate cancer", "hormone sensitive prostate cancer", "castrate", "non castrate", "androgen deprivation therapy", "chemotherapy", "docetaxel", "hormone resistance", "castrate resistance", "phase III", and "randomized study". We assessed the quality of evidence by methods used, with the highest quality attributed to randomised studies. We identified two randomised trials[9,10] that showed that chemotherapy—namely docetaxel—could improve survival in patients with metastatic castration-resistant prostate cancer. Additionally, we identified 11 randomised trials of castration with or without chemotherapy other than docetaxel in patients with metastatic non-castrate (ie, hormone-sensitive) prostate cancer. None of these trials showed improvement in survival. We obtained up-to-date information from abstracts and congress presentations on Current Contents and Web of Science. Information about studies that are in progress was gathered from the Physician Data Query NCI's list of cancer clinical trials.

Interpretation

As far as we are aware, ours is the first phase 3 trial to have assessed docetaxel chemotherapy in patients with metastatic non-castrate prostate cancer. As has been previously described with other cytotoxic drugs, the addition of docetaxel to androgen-deprivation therapy did not improve survival compared with androgen-deprivation therapy alone in metastatic non-castrate prostate cancer in our study.

underwent radical prostatectomy for localised prostate cancer, are also awaited.

Discontinuation of docetaxel in our study was mainly because of toxic effects. In the TAX 327 study,[9] a smaller proportion of patients (11%) treated with docetaxel every 3 weeks stopped treatment because of adverse events than in our study. However, a proportion similar to that in our study discontinued treatment due to adverse events with docetaxel plus prednisone at the same doses (22%) in the CALGB 90401 phase 3 study.[25]

Our data show that adverse events after docetaxel treatment should be closely monitored, and the frequency of severe neutropenia should be limited by granulocyte colony-stimulating factor. Before the amendment of the study protocol to allow administration of granulocyte colony-stimulating factor, grade 3–5 neutropenia was noted in almost a third of patients, 7% of patients had febrile neutropenia, and two patients died from neutropenia-related conditions. However, after the amendment, the frequency of neutropenia and febrile neutropenia of grade 3–4 decreased substantially and no subsequent toxic deaths occurred. Febrile neutropenia after docetaxel treatment was more frequent in our study than in previous trials of metastatic castration-resistant prostate cancer (3% in TAX 327[9] and 4·2% in CALGB 90401[25]) or in the neoadjuvant setting in high-risk localised prostate cancers (2% in GETUG 12[22]). Previous reports[26–28] have suggested that the frequency of severe neutropenia is reduced in castration-resistant prostate cancer compared with non-castrate prostate or non-prostate cancer. This finding might be explained by a decreased docetaxel exposure in metastatic castration-resistant prostate cancer:[29] Docetaxel clearance is increased by about 100% in men with castration-resistant prostate cancer compared with those with non-castrate disease, and is associated with a two-fold reduction in the area under the curve, although hepatic activity of cytochrome P450 3A4 is unchanged (p=0·0001), probably because of an increase in hepatocyte uptake.

Our study has limitations. We might not have had sufficient power to show a small difference in overall survival—if any—because we underestimated overall survival in the ADT group, and were overoptimistic in terms of potential difference in survival when we did our sample size calculation. Additionally, we do not have information about response to docetaxel (either first docetaxel treatment for patients previously treated with ADT alone or rechallenge in those who had received ADT plus docetaxel).

In summary, we showed that the addition of chemotherapy to ADT does not provide a benefit in terms of overall survival compared with ADT alone, although bPFS, cPFS, and PSA response were improved. Although quality of life was impaired during docetaxel treatment, global scores at 12 months were generally similar in the two groups. Overall, our results suggest that docetaxel should not be added to ADT in first-line treatment for metastatic non-castrate prostate cancer.

Contributors

All authors contributed to data collection, data analysis, data interpretation, and writing or review of the report. All authors approved the final version.

Conflicts of interest

GG has participated in advisory boards for Sanofi-Aventis and been a speaker for Amgen, AstraZeneca, and Sanofi-Aventis. KF has participated in advisory boards or been a speaker, or both, for Amgen, AstraZeneca, Novartis, Sanofi-Aventis, Keocyt, Ipsen, Janssen, Astellas and Medivation, Bristol-Myers Squibb, Algeta, and Bayer. FJ has participated in advisory boards for Sanofi-Aventis. SO has received honoraria from Pfizer, Sanofi-Aventis, Roche, Novartis, Keocyt, and Bayer; and research grants from Sanofi-Aventis and Keocyt. BL has received honoraria from Sanofi-Aventis. JMF has received honoraria from Pfizer, Sanofi-Aventis, and Novartis. DP has received honoraria from Sanofi-Aventis and Amgen, and has been a speaker for Sanofi-Aventis. JCE has received honoraria for being a board member for Sanofi-Aventis. The other authors declare that they have no conflicts of interest.

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