TAXOMET: A French Prospective Multicentric Randomized Phase II Study of Docetaxel Plus Metformin Versus Docetaxel Plus Placebo in Metastatic Castration-Resistant Prostate Cancer

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Abstract

MET could increase the cytotoxicity effect of DOCE against PC3 prostate cancer cells and reduce cancer-related mortality in *retrospective study*. TAXOMET study randomized 99 non-diabetic metastatic castration-resistant prostate cancers: 50 pts in docetaxel-metformin combination vs. 49 patients in docetaxel plus placebo. With a median follow-up of 86 months, MET addition failed to improve the standard DOCE regimen.

Background: Docetaxel (DOCE) is a standard of care in metastatic castration-resistant prostate cancer (mCRPC). Several retrospective studies suggested a decrease in Prostate Cancer incidence and mortality with metformin (MET). MET has also demonstrated anti-tumor activity in Prostate Cancer preclinical models, with increased apoptosis when added to DOCE. We aimed at exploring the role of MET in combination with DOCE in mCRPC. **Patients and Methods:** Non-diabetic mCRPC patients were randomly assigned to receive DOCE 75 mg/m^2 every 21 days + prednisone (5 mg. BID) with either MET 850 mg BID (D+M) or placebo (D+P) up to 10 cycles. Prostate-Specific Antigen (PSA) response ≥50% from baseline was the primary end point. Secondary end points included objective response rate (ORR), progression-free survival (PFS), overall survival (OS), toxicity and quality of life (QoL). **Results:** Out of 99 patients were randomized (D+M = 50; D+P = 49) in 10 French centers. The median follow-up was 86 (IQR 73-88) months. The PSA-response rate reached 66% in the D+M arm, but was not different from that observed in the D+P arm (63%, *P = 0,94*). In the D+M and D+P arms, the ORR was 28% and 24%, the median PFS was 7.8 and 6.0 months and the median OS was 27 and 20 months (ns), respectively. Diarrhea grade I to II was more frequent in the MET arm (66% vs. 43%). No impairment of QoL was observed. **Conclusion:** MET addition failed to improve the standard DOCE regimen in mCRPC. Further research targeting tumor cell metabolism should be performed.

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Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related death among men in the United States[1] and the third leading cause of cancer-related death in Europe.[2] Advanced PCa is initially considered hormone-sensitive and usually progresses to a castration-resistant state after a median time of 3 years.[3] Docetaxel (DOCE) was the first agent to significantly extend survival in castration-resistant metastatic prostate cancer (mCRPC).[4, 5] DOCE remained the backbone standard of care for the development and approval of other life-prolonging drugs such as abiraterone[6, 7], enzalutamide[8, 9] and cabazitaxel.[10] The evaluation of drugs combination with DOCE is still ongoing.

Metformin (MET) is a hypoglycemic agent widely used to treat type II diabetes. MET has shown an anti-tumor effect in various solid cancer types, particularly in PCa.[11] The prospective ZODIAC-16 study demonstrated a dose-dependent reduction of cancer-related mortality in diabetic MET users.[12]

Since the early 2000s, preclinical studies showed that MET might influence cancer cell proliferation[13] and reduce metastatic spread[14] through two distinct mechanisms: (1) direct effect (insulin-independent) by blocking the cell cycle in G0/G1 phase.[15] This effect could be mediated by a decrease in cyclin D1 level, leading to downregulate the mammalian target of rapamycin pathway[16]; (2) indirect effect (insulin-dependent) with inhibition of hepatic gluconeogenesis[17], decrease of insulin secretion and downregulation the phosphoinositide 3-kinase (PI3K) axis.

MET proved to be an effective chemosensitizer for DOCE, reducing PC3 cell migration and viability[18] and negating hyperglycemia-induced resistance to DOCE in androgen-independent cell lineages in normo- and hyperglycemia condition.[19] In early-stage breast cancer, diabetic patients receiving MET and neoadjuvant chemotherapy had a higher pathologic complete response rate than patients treated with chemotherapy alone.[20] In diabetic patients with advanced non-small cell lung cancer and advanced endometrial cancer, MET addition to chemotherapy improved survival.[21, 22]

These preliminary results prompted us to evaluate the efficacy of MET and DOCE combination in non-diabetic mCRPC patients.

Methods

Patients

The study enrolled male patients aged 18 years or older with a histologically confirmed adenocarcinoma of the prostate, with evidence of metastatic disease progression under androgen deprivation therapy (ADT), with serum testosterone levels ≤50 ng/dL. Disease progression was defined by at least one of the following conditions: (1) an increasing serum level of PSA on three consecutive measurements obtained at least one week apart (with a minimal value of 2 ng/mL at the enrollment) or (2) a progression on CT scan according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) or (3) a progression on bone scan with appearance of ≥2 new lesions during ADT, according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2)[23]. Patients were required to have an Eastern Cooperative Oncology Group performance status of ≤2 and adequate organ and bone marrow function. Antiandrogen medication had to be withdrawn for at least 28 days before randomization. Main exclusion criteria included previous cytotoxic treatment, diabetes, brain metastases, peripheral neuropathy ≥grade III and radiotherapy within 4 weeks before enrollment.

Study Design

TAXOMET is a randomized, double-blind, phase II study. Patients were enrolled in 10 French centers from January 2013 to May 2018, and randomly assigned at a 1:1 ratio to either DOCE plus MET (D+M) or DOCE plus placebo (D+P). DOCE 75mg per square meter (m^2) of body-surface area was administrated intravenously as a 1-hour infusion every 21 days. All patients received 5 mg of prednisone (or prednisolone) orally twice daily starting on day 1. Premedication included methylprednisolone at 60mg before DOCE on day 1. Antiemetic medication and primary prophylactic granulocyte-colony stimulating factor were prescribed at physician's discretion. MET or placebo was administered orally at 850mg twice daily, as previously described.[24] Up to 10 cycles of treatment were planned. A DOCE delay or dose reduction (60 mg/m^2) was allowed for patients with an absolute neutrophil count of less than 1500 per cubic millimeter and for those with grade III or IV thrombocytopenia. A permanent discontinuation was planned in patients who had a grade IV neutropenia or febrile neutropenia, a grade IV thrombocytopenia or a grade III neuropathy. MET or placebo was also discontinued in case of DOCE interruption. Dose reduction was not allowed for MET or placebo. Because of drug interaction, furosemide, nifedipine and angiotensin converting enzyme inhibitors were forbidden. MET was discontinued in case of lactic acidosis, hepatic impairment or renal failure with a creatinine clearance lower than 30 ml/mn according to Cockroft-Gault formula. ADT had to be maintained during the study. All patients provided written informed consent. The study was approved by the local ethic committee at each participating site and conducted in accordance with Good Clinical Practice guidelines and the Helsinki Declaration.

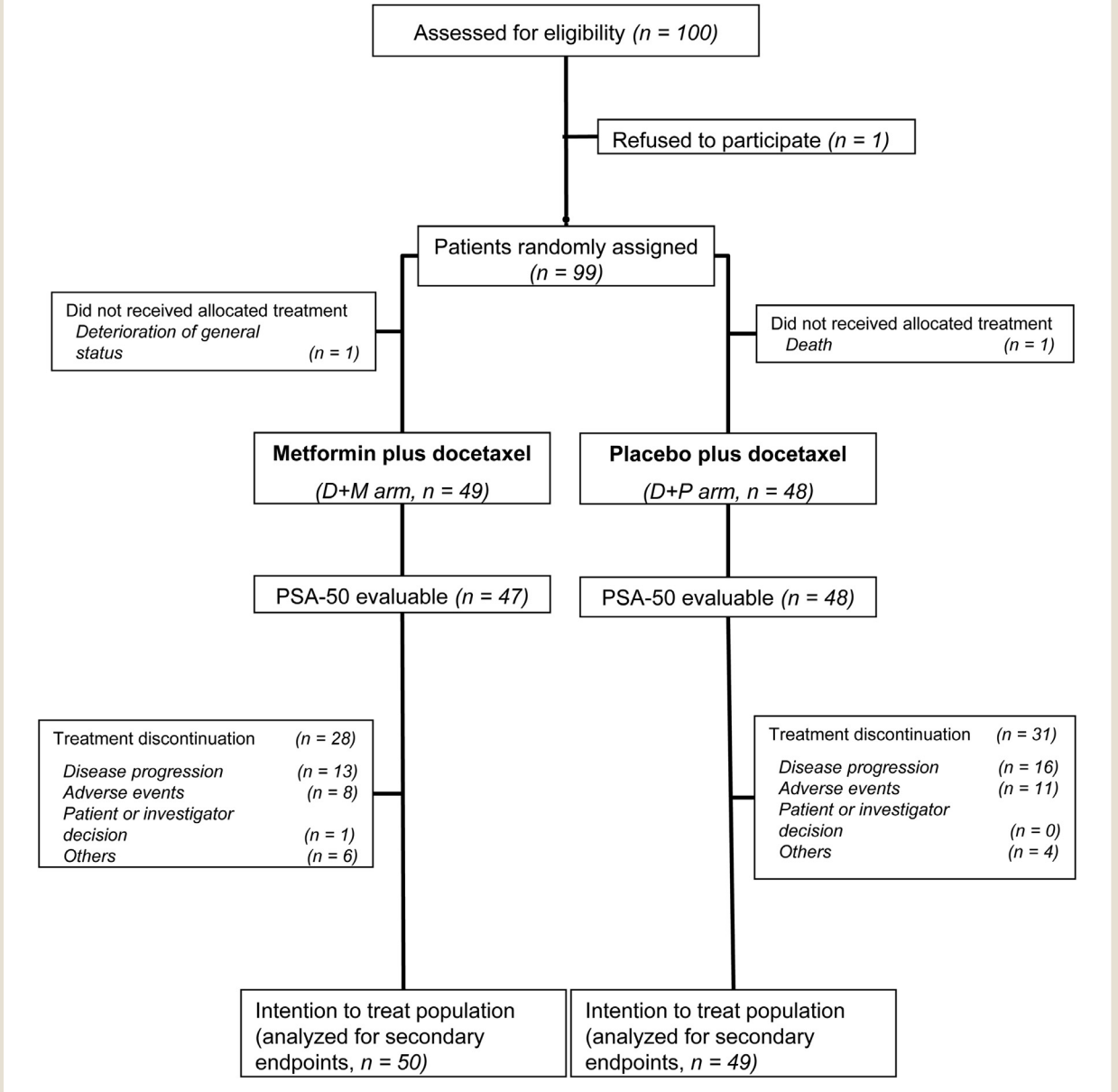
Endpoints

The primary end point was the PSA response rate, as defined by the PCWG2 criteria.[23] PSA was measured at baseline, every three weeks during the treatment period and every three months thereafter. A PSA response was defined as a reduction of at least 50% from the baseline value (PSA-50), whereas PSA progression was defined as an increase from the nadir of either at least 25% for men with no PSA response or at least 50% for all others.

Secondary end points were the time to PSA nadir, the objective response rate (ORR), the progression-free survival (PFS), overall survival (OS) and safety. Time to PSA nadir was the time between randomization and PSA nadir. PFS was defined as the time from randomization to PSA, radiological and/or clinical progression, or death by any cause. The ORR was evaluated with a contrast-enhanced CT scan according to RECIST v1.1[25] and bone scan according to PCWG2 criteria. Imaging was performed at the baseline and every 12 weeks thereafter. Overall survival was defined as the time from randomization to death of any cause.

Safety assessments included monitoring of adverse events (AEs) or deaths, standard laboratory test results, and physical examination findings. Safety was assessed at least every 3 weeks during the treatment, and at least every 12 weeks thereafter. Adverse events were

Figure 1 TAXOMET CONSORT Diagram.



classified according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

Prespecified exploratory endpoints included quality of life (QoL) using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module (EORTC QLQ-C30) form at baseline, at cycle 6 and at the end of the treatment. All patients who answered the questionnaire at baseline were included in the evaluation and the subsequent QLQ-C30 score was compared with the baseline value for each patient.

Statistical Analysis

On the basis of 45%, CI95% [40-51] of PSA-50 rate with DOCE in the TAX327 trial[4], we assumed that DOCE plus MET had no therapeutic interest if PSA-50 response rate was 40% or lower (H0), whereas a PSA-50 response rate of at least 60% would define a clinical activity (H1).

The number needed to treat was calculated using the Fleming one-step design with a one-sided alpha error of 5%, and 95% power, and with chosen thresholds of 40% and 60%. As a result, 47 patients were required in each group. Assuming that 5% of patients would

Table 1 Baseline Characteristics in the Intention to Treat Population

	Docetaxel + Metformin *N = 50*	Docetaxel + Placebo *N = 49*
Median Age, years [range]	70 [54-84]	69 [49-83]
Median BMI, kg/m^2 [IQR]	27.2 [24.4-29.5]	26.1 [24.6-28.2]
PS, n (%)		
0	25 (50)	17 (35)
1	24 (48)	28 (57)
2	1 (2)	4 (8)
Gleason Score, n (%)		
6	6 (12)	8 (16)
7	13 (26)	16 (33)
≥ 8	30 (60)	23 (47)
Unknown	1 (2)	2 (4)
Site of metastases, n (%)		
Lymph node	26 (52)	25 (51)
Bone	36 (72)	37 (76)
Visceral	12 (24)	11 (22)
Lung	7 (14)	7 (14)
Liver	5 (10)	4 (8)
Others	1 (2)	1 (2)
Number of previous hormonal therapies, n (%)		
1	18 (36)	14 (29)
2	23 (46)	20 (41)
≥3	9 (18)	15 (30)
Previous Abi or Enza, n (%)		
Abiraterone acetate	9 (18)	9 (18)
Enzalutamide	1 (2)	0 (0)
Others	1 (2)	2 (4)
Median baseline PSA, ng/mL [range]	80.3 [5.1-11,378]	54.5 [2.5-3,291]
Median Time to progression to CRPC, months [range]	7.45 [0.50-60.60]	14.8 [0.30-131.40]

Abbreviations: Abi = abiraterone acetate; BMI = body mass index; CRPC = castration resistant-prostate cancer; Enza = enzalutamide; IQR = interquartile range; PS = performance status

not be evaluable, the number of patients to include was 50 patients in each group.

PFS and OS were sketched by Kaplan-Meier plots, after a median follow-up of 5 years. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using Cox model and were provided on an indicative basis only.

Qualitative data were analyzed with Chi2 test or Fisher's test in case of non-compliance with Chi2 test requirements. Quantitative data were analyzed with Student's t-test or Mann-Whitney's test in case of non-compliance with Student's test requirements.

Comparative results between the D+M arm and the D+P arm were provided for information purposes only.

RESULTS

Patients

Between January 2013 and December 2015, 99 patients were enrolled in 10 French sites. Fifty patients were assigned to D+M arm and 49 were assigned to D+P arm. One patient in the D+P arm withdrew consent and was not included in the analysis (see consort diagram in **Figure 1**). The median follow-up in the overall study population was 86 months (IQR 73-88 months).

Patient's characteristics are summarized in **Table 1** . The two arms were well balanced, for prognostic factors with the exception of the Gleason score ≥8 (60% in the D+M arm vs. 47% in the D+P arm) and the median baseline PSA level (80.3 ng/mL for D+M vs. 54.5 ng/mL for D+P).

Treatment exposure is summarized in **Table 2** . The median number of treatment cycles was 7 in both arms. Less than 40% of patients in each arm reached the 10 cycles. DOCE dose reduction were required for 4 (8%) patients in the D+M arm and 7 (15%) in the D+P arm. G-CSF prophylaxis was used for 28% and 24% of patients with D+M and D+P, respectively.

Discontinuation because of AEs and progressive disease were more common with D+P (22% and 33%) than with D+M (16% and 26%).

Efficacy

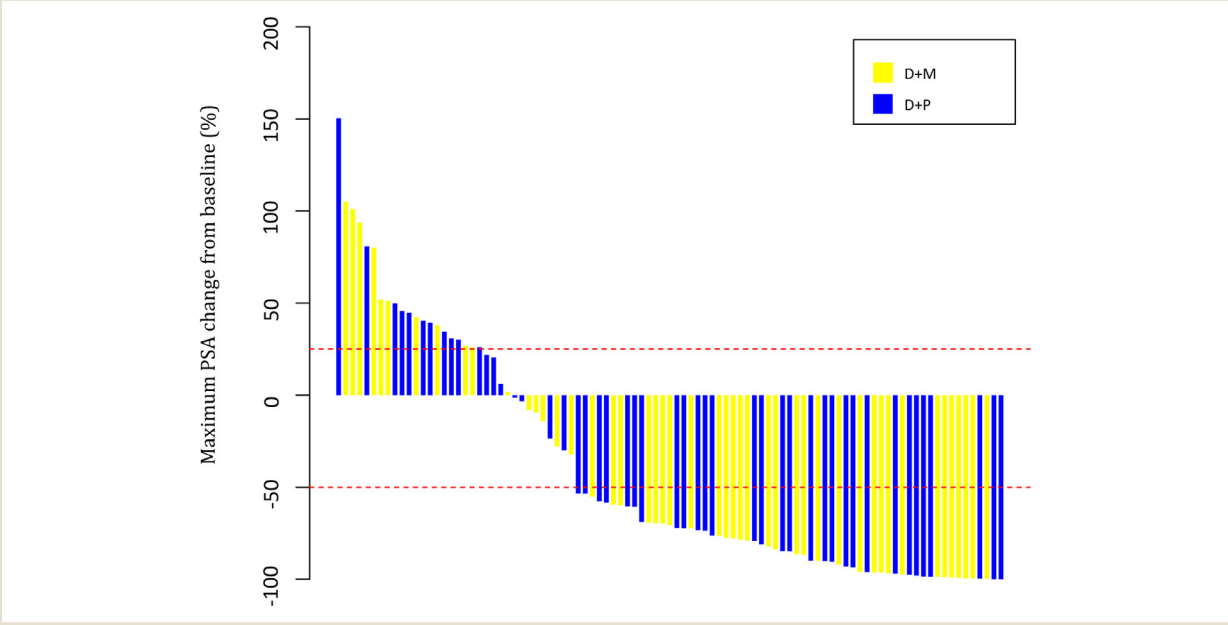
The PSA-50 response rate (primary end point) was similar between treatment arms: 66% in the D+M arm (47 evaluable patients) and 63% in the D+P arm (48 evaluable patients), $P = .94$ (**Figure 2**). Time to PSA nadir was 4.8 months, CI95% [2.1-6.5] vs. 4.6 months, CI95% [1.9-6.5] in D+M and D+P respectively, $P = .75$.

Table 2 Treatment Exposure

	Docetaxel+Metformin N = 50	Docetaxel+Placebo N = 49
Metformin/Placebo exposure		
Median treatment duration, days [range]	145 [1-224]	148 [7-218]
Relative dose-intensity in % [range][a]	99 [50-100]	99 [10-100]
Docetaxel exposure		
Median number of cycles per patient [range]	7 [0-10]	7 [0-10]
Up to 6 cycles, n (%)	29 (58)	36 (73.5)
Up to 10 cycles n (%)	19 (38)	18 (36.7)
Number of patients with at least 1 dose		
reduction, n (%)	4 (8)	7 (15)
G-CSF n (%)	14 (28)	12 (24)
Treatment discontinuation, n (%)		
Maximal clinical benefit	22 (44)	18 (37)
Disease progression	13 (26)	16 (33)
Adverse events	8 (16)	11 (22)
Patient or investigator decision	1 (<1)	0
Others	6 (12)	4 (8)

Abbreviation: G-CSF = granulocyte stimulating factor
[a] The ratio of metformin or placebo dose delivered rate to metformin or placebo dose planned during the treatment.

Figure 2 Waterfall plot for best PSA response. D+M: Docetaxel + Metformin. D+P: Docetaxel + Placebo.



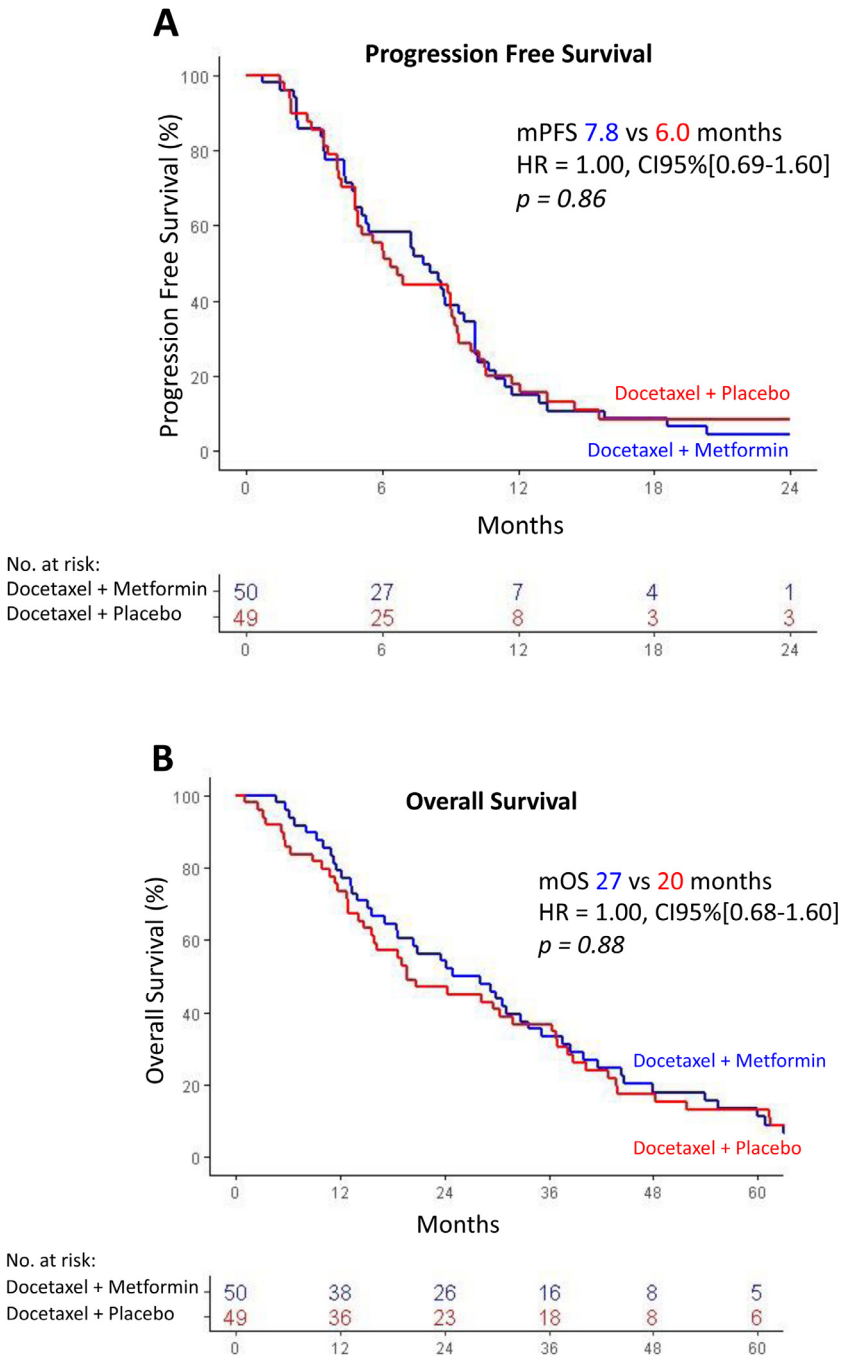
ORR was 28% in the D+M arm (43 evaluable patients) and 24% in the D+P arm (45 evaluable patients), $P = .90$.

Median time to PSA progression was 8.7 months in the D+M arm, CI95%[7.3-10.0] and 9.2 months in the D+P arm, CI95%[6.7-12.0], HR 0.82, CI95%[0.52-1.30], $P = .40$.

In the ITT analysis, a total of 93 PFS events (47 in D+M, 46 in D+P) and 92 OS events (46 in both arms) occurred in the randomized patient population. Median PFS was 7.8 months, CI95% [5.1-9.6] in the D+M arm and 6.0 months CI95% [4.8-9.1] in the D+P arm (HR = 1.00, CI95% [0.69-1.60], $P = .86$) (Figure 3 **A**). Median OS was 27 months, CI95% [19-35] in the D+M arm and 20 months CI95% [16-37] in the D+P (HR = 1.00, CI95% [0.68-1.60], $P = .88$) (Figure 3 **B**).

Death occurred because of disease progression ($n = 81$), septic shock not related to treatment 14 and 15 months after DOCE discontinuation ($n = 2$), nosocomial infection 13 months after

Figure 3 Kaplan Meier estimates of progression free-survival (A) and overall survival (B). *HR and P value were provided on an indicative basis only.*



DOCE ($n = 1$), subdural hematoma ($n = 1$), catheter related infection 9 months after DOCE discontinuation ($n = 1$), thromboembolic disease ($n = 1$), 4 deaths for unknown reason ($n = 4$) and one suicide ($n = 1$).

Safety

There was no clinically relevant difference in the grade III-IV safety profile between the two arms. An expected increased incidence of all-grade diarrhea with MET (72% in the D+M arm vs. 49%

Table 3 Summary of Frequently-Reported Aes Occurring in ≥5% Of Patients in Either Treatment Group (Safety Analysis Set)

Adverse event	Docetaxel+Metformin (N = 50)		Docetaxel+Placebo (N = 49)	
	Any Grade, n (%)	Grade III-IV, n (%)	Any Grade, n (%)	Grade III-IV, n (%)
Any events	50 (100)	22 (44)	49 (100)	28 (57)
Asthenia	34 (68)	7 (14)	36 (73)	6 (12)
Alopecia	23 (46)	3 (6)	28 (57)	3 (6)
Musculoskeletal disorders	19 (38)	2 (4)	19 (39)	3 (6)
Diarrhea	36 (72)	3 (6)	24 (49)	3 (6)
Constipation	5 (10)	1 (2)	12 (24)	0 (0)
Abdominal pain	6 (12)	1 (2)	11 (22)	0 (0)
Decreased appetite	12 (24)	1 (2)	8 (16)	0 (0)
Dysgeusia	13 (26)	0 (0)	9 (18)	0 (0)
Stomatitis	6 (12)	0 (0)	7 (14)	1 (2)
Vomiting	5 (10)	1 (2)	12 (24)	4 (8)
Hematuria	4 (8)	0 (0)	1 (2)	0 (0)
Headache	3 (6)	0 (0)	8 (16)	0 (0)
Febrile neutropenia	0 (0)	0 (0)	6 (12)	6 (12)
Neutropenia	7 (14)	5 (10)	8 (16)	6 (12)
Anemia	16 (32)	1 (2)	16 (33)	2 (4)
Blood LDH increased	4 (8)	0 (0)	9 (18)	0 (0)
GGT increased	3 (6)	1 (2)	5 (10)	0 (0)

Abbreviations: GGT = gamma-glutamyltranspeptidase; LDH = lactate dehydrogenase

in the D+P arm) was observed without difference in grade III-IV (6% in each arm). Some AEs were more commonly observed in the D+P arm, among which constipation, abdominal pain, vomiting and febrile neutropenia. Conversely, decreased appetite and dysgeusia were more commonly observed in the D+M arm (**Table 3**). No toxic death occurred in this study.

Quality of Life

At baseline, 98% of patients completed the EORTC QLQ-C30 questionnaire in both arms, compared to 54% vs. 69% after cycle 6, and 66% vs. 65% at the end of the treatment in the D+M arm vs. the D+P arm, respectively. No difference in global health status was observed between baseline and the 6th cycle of DOCE or between baseline and the end of the treatment (**Figure 4**).

Discussion

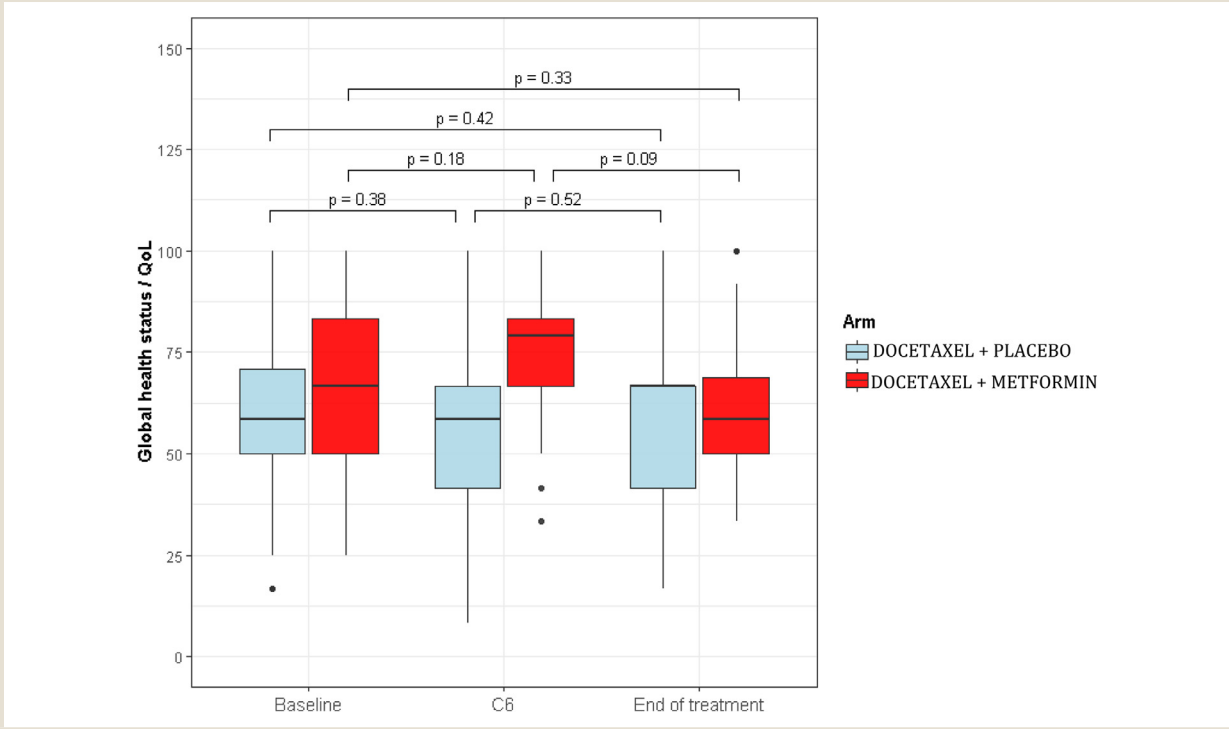
DOCE was shown to be the first known agent to prolong survival in patients with mCRPC. Further therapies have been investigated in mCRPC patients, before or after DOCE-based treatment, alone or in combination with DOCE. However, among all DOCE-based combination studies, none so far improved survival compared to DOCE alone.[26] In the past few years, an increasing number of controversial reports have been published on the effect of MET on PCa treatment outcome.[27] These data have raised the question of the potential benefit of MET-based treatment to improve outcome in PCa, with a suggested favorable toxicity profile.

TAXOMET is the first prospective randomized trial reporting the effect of the addition of MET to standard first-line DOCE and prednisone chemotherapy in mCRPC. The characteristics of the patients, the median number of cycles (7) and the median overall survival in TAXOMET were comparable to the previous reported DOCE-based trials TAX327[4] and SWOG-99-16[5]. As expected, the safety profile of MET was consistent with that previously reported, with a higher incidence of grade I or II diarrhea in the D+M arm. No QoL impairment was observed in neither arm.

The primary end point PSA-50 was reached with D+M treatment as well as in the control arm (D+P). However, PSA-50 results in D+P arm were better than expected based on TAX327 study (63% in TAXOMET and 45% in TAX327). Addition of MET to DOCE did seem to improve PSA response, PFS or OS compared to DOCE alone. These findings were in agreement with the retrospective cohort of 2832 mCRPC patients who received DOCE (1226 non diabetic, 359 taking MET, 1102 taking other antidiabetic medication). The prostate cancer specific survival results between no-diabetes group and MET-users with or without other diabetes drugs were similar (HR = 0.96, $P = .66$) [28].

Despite similar outcomes between the two arms, some prognostic factors were unbalanced including Gleason score and PSA baseline value, raising the question of the real impact of MET in this population. Additionally, both MET and DOCE were discontinued after a maximum of 10 cycles. Thus, the study design did not provide information about a potential role of MET in maintenance after the end of DOCE. In the current study, body fat mass, insulin level or C-peptide level were not evaluated because the direct anti-tumor activity of MET was tested in a non-diabetic population, which can explain the lack of results. Indeed, insulin could increase intratumoral androgen production in PCa[29] but the optimal regulation of circulating insulin could explain the lack of impact of MET. Some

Figure 4 QoL: Boxplot of the QLQ-C30 questionnaire at baseline, at cycle 6 and at the end of the treatment
P values were provided on an indicative basis only.



retrospective and meta-analysis data suggested that the survival benefit with MET could be preferentially observed in diabetic MET users.[30, 31]

The PSA decline as a surrogate endpoint for survival has never been formally assessed. Nevertheless, in the TAX327 study the rate of PSA response was significantly higher ($P < .001$) in the DOCE group than in the mitoxantrone group. Similarly, MET induced an objective PSA response in the phase II SAKK 08/09 trial, which aimed to assess the effect of MET on PFS and PSA doubling time in patients with CRPC.[32] These results prompted us to adopt PSA decline as the main endpoint in TAXOMET.

Evaluation of MET may also be evaluable in hormone-sensitive prostate cancer population. A randomized controlled trial demonstrated that combining MET to ADT increased castration-resistant prostate cancer-free survival by 9 months compared to ADT alone (29 vs. 20 months; $P = 0,01$).[33] A meta-analysis suggested that the addition of MET to ADT improved PCa-specific survival and overall survival, which could suggest a greater sensitivity to MET in hormone-sensitive prostate cancer population.[27] MET could potentiate the efficacy of ADT and extend the cell death effects of bicalutamide.[34, 35]

Despite no formal clinical benefit in our study, MET may be useful in patients with mCRPC. More than 50% of men under long-term ADT develop a metabolic syndrome, which is an important factor for biochemical failure after prostatectomy and radiotherapy.[36] MET exhibited therapeutic benefits for weight gain induced by insulin resistance.[27] Through the treatment of the diabetes-associated metabolic syndrome, MET may represent an important actor of multimodal strategy for PCa patient treated with ADT.

Overall, D+M is active and well tolerated in patients with mCRPC. However, the PSA response was similar in D+M and D+P groups. MET might not improve DOCE regimen in mCRPC population.

Clinical Practice Points

- Synergistic drug combination with docetaxel to treat metastatic castration-resistant prostate cancer (mCRPC) still remains a large area of research.
- Metformin (Met) showed an anti-tumor effect in *preclinical studies* with castration-resistant prostate cancer cell lineage and xenograft model and it proved to be an effective chemosensitizer for docetaxel. In retrospective studies, Met seem to reduce cancer-related mortality especially in prostate cancer.
- TAXOMET is the first randomized clinical trial studying Met associated with docetaxel versus docetaxel plus placebo in non-diabetic mCRPC.
- Met-docetaxel combination did not show any benefit in Prostate-Specific Antigen (PSA) response, in progression free-survival and in overall survival.
- Unfortunately, TAXOMET becomes another addition to previous negative clinical trial that assessed docetaxel in combination in mCRPC.

Disclosure

Delphine Borchiellini is a principal investigator/subinvestigator of clinical trials for AstraZeneca, BMS, Exelixis, Infinity, Janssen, Merck KGaA, MSD, Novartis, Pfizer and Roche and reports personal fees from AstraZeneca, BMS, MSD, Novartis, Pfizer and Roche. Werner Hilgers has received honoraria from AstraZeneca, BMS, Janssen, Roche, MSD, has served as consultant to AstraZeneca and Janssen. Benjamin Hoch has received honoraria and served to consultant to Janssen and Pfizer. Jean-Baptiste Paoli has received research funding from MSD and BMS. Jean-Laurent Deville has received honoraria from Janssen, Sanofi, BMS and MSD; has served as consultant to Janssen and BMS; has received research support from Janssen, Basilea, Astellas, Merck, MSD, Aztrazeneca, Inciye. Jean-Marc Ferrero has received honoraria from Pfizer, Novartis, Lilly and Esai. All remaining authors have declared no conflicts of interest.

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Pujalte Martin Marc: Validation, Writing – original draft. Borchiellini Delphine: Investigation, Validation, Writing-Review & Editing. Thamphya Brice: Formal Analysis. Guillot Aline: Investigation. Paoli Jean-Baptiste: Investigation. Besson Dominique: Investigation. Hilgers Werner: Investigation. Priou Frank: Investigation. El Kouri Claude: Investigation. Hoch Benjamin: Investigation. Deville Jean-Laurent: Investigation. Schiappa Renaud: Software, Validation, Project administration. Cheli Sandrine: Supervision, Project administration. Milano Gérard: Writing Review & Editing. Tanti Jean-François: Conceptualization. Bost Frédéric: Methodology, Writing Review & Editing. Ferrero Jean-Marc: Conceoptualization, Methodology, Investigation, Funding aciquisition, Validation, Writing - review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2021.08.008.

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