TAXOMET : A French prospective multicentric randomized controlled phase II study comparing docetaxel plus metformin versus docetaxel plus placebo in mCRPC

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Abstract:	BACKGROUNG Docetaxel (DOCE) is a standard of care in metastatic castration-resistant prostate cancer (mCRPC). Several retrospective cohort studies suggest a decrease in Prostate Cancer (PCa) incidence and mortality with metformin (MET). MET has also demonstrated anti-tumor activity in PCa preclinical models, with increase apoptosis when added to DOCE. The addition of MET could enhance DOCE efficacy in mCRPC patients (pts). METHODS TAXOMET is a phase II, prospective multicentric randomized controlled trial. Non-

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	diabetic mCRPC pts were assigned 1:1 to receive DOCE 75mg/m2 every 21 days + prednisone (5mg BID) and either MET 850mg BID (D+M) or placebo (D+P), up to 10 cycles. The primary end point was PSA response rate (≥50% decrease from baseline). Main secondary endpoints included objective response rate (ORR, according to RECIST v1.1), clinical, biological and/or radiographic progression-free survival (PFS), overall survival (OS), toxicity and quality of life (QoL). Comparisons between arm D+M and D+P were performed using Chi2 test for qualitative data and Log-rank test for survival data. RESULTS From January 2013 to December 2015, 99pts were randomized (50 in D+M and 49 in D+P arm) in 10 french centers and 95pts were evaluable. No difference was observed between D+M and D+P arm in PSA-response rate (66% vs 63%), ORR (28% vs 24%), mPFS (7.8 vs 6.0 months p= 0.70) and mOS (24.6 vs 19.7 months, p= 0.70), respectively. There was no difference in adverse events, except more diarrhea with MET (70% vs 50%, p = 0.072). No degradation of QoL was observed in both arms. CONCLUSION This is the first prospective randomized controlled trial to evaluate the combination of MET with DOCE in mCRPC. The addition of MET has no meaningful clinical benefit in this setting.
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Dear Editorial Board,

Please find enclosed an original report entitled « TAXOMET : A French prospective multicentric randomized controlled phase II study comparing docetaxel plus metformin versus docetaxel plus placebo in mCRPC».

The results of this prospective randomized, double-blinded, phase 2 study were presented in oral session at the ASCO meeting 2019.

For a long time, metformin, an oral hypoglycaemic agent, has been suggested to have a potential anti-cancer effect in prostate cancer. In vivo studies suggested synergistic effect of metformin associated with docetaxel.

The TAXOMET study was designed to assess the efficacy of the association of metformin plus docetaxel in non-diabetic mCRPC patients. The study did not point out any significant benefit of metformin either in PSA response, PFS or OS, when combined to docetaxel, compared to docetaxel plus placebo.

The safety profile was acceptable, with more grade 1-2 diarrhea with metformin, but no difference in grade 3-4 AEs, and no deterioration in quality of life.

We think that these results will be of interest for the oncologic community and deserve to be published, to reconsider the use of metformin in prostate cancer.

This work has not been submitted for publication elsewhere.

We hope the present manuscript could be published in your journal.

Sincerely,

Dr. Delphine Borchiellini

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ABSTRACT

BACKGROUNG

Docetaxel (DOCE) is a standard of care in metastatic castration-resistant prostate cancer (mCRPC). Several retrospective cohort studies suggest a decrease in Prostate Cancer (PCa) incidence and mortality with metformin (MET). MET has also

demonstrated anti-tumor activity in PCa preclinical models, with increase apoptosis when added to DOCE. The addition of MET could enhance DOCE efficacy in mCRPC patients (pts).

METHODS

TAXOMET is a phase II, prospective multicentric randomized controlled trial. Non-diabetic mCRPC pts were assigned 1:1 to receive DOCE 75mg/m2 every 21 days + prednisone (5mg BID) and either MET 850mg BID (D+M) or placebo (D+P), up to 10 cycles. The primary end point was PSA response rate (≥50% decrease from baseline). Main secondary endpoints included objective response rate (ORR, according to RECIST v1.1), clinical, biological and/or radiographic progression-free survival (PFS), overall survival (OS), toxicity and quality of life (QoL). Comparisons between arm D+M and D+P were performed using Chi2 test for qualitative data and Log-rank test for survival data.

RESULTS

From January 2013 to December 2015, 99pts were randomized (50 in D+M and 49 in D+P arm) in 10 french centers and 95pts were evaluable. No difference was observed between D+M and D+P arm in PSA-response rate (66% vs 63%), ORR (28% vs 24%), mPFS (7.8 vs 6.0 months p= 0.70) and mOS (24.6 vs 19.7 months, p= 0.70), respectively. There was no difference in adverse events, except more diarrhea with MET (70% vs 50%, p = 0.072). No degradation of QoL was observed in both arms.

CONCLUSION

This is the first prospective randomized controlled trial to evaluate the combination of MET with DOCE in mCRPC. The addition of MET has no meaningful clinical benefit in this setting.

KEYWORDS
Metformin, docetaxel, metastatic castration-resistant, prostate cancer

RUNNING TITLE
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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, depending on androgen receptor (AR), and classically progresses to a castration-resistant (CR) state after a median time of 3 years[3]. Docetaxel was the first agent to significantly extend survival in men with metastatic castration resistant prostate cancer (mCRPC)[4,5]. Ever since, docetaxel has been the backbone for the development and approval of other life-prolonging drugs abiraterone[6,7], enzalutamide[8,9] and cabazitaxel[10]. To further improve survival in mCRPC, synergistic combination of docetaxel with other drugs has been a main research area.

Metformin, a well-tolerated oral hypoglycemic agent, commonly used as a first-line treatment for type II diabetes, has shown to have an anti-tumor effect in various solid cancers, particularly in PCa[11]. Metformin inhibited PCa cell proliferation and tumor growth in animal models by blocking the cell cycle in G0/G1 phase[12] through a decrease of cyclin D1 level, along with a downregulation of the Mechanistic Target Of Rapamycin (mTOR) pathway, independently of AMP-activated protein kinase (AMPK) pathway[13]. In addition, metformin alone reduces the formation of PCa metastasis in animal models[14]. Metformin combined with other chemotherapy could improve anticancer effect and/or allow dose reduction to decrease toxicity. *In vitro*, metformin seemed to be an effective chemosensitizer for docetaxel, reducing PC3 cell migration and cell viability[15]. In early stage breast cancer, diabetic patients receiving metformin and neoadjuvant chemotherapy had a higher pathologic complete response rate than diabetics not receiving metformin[16]. Metformin, when used concurrently with chemotherapy, seemed also to improve survival in diabetic patients with advanced non-small cell lung cancer and advanced endometrial cancer[17,18].

In patients with PCa, metformin use seemed to be associated with a decreased risk of PCa diagnosis and progression, while an increased cumulative duration of metformin exposure after PCa diagnosis was associated with a reduction in both all-cause and PCa-specific mortality among diabetic men[19,20]. Metformin has also been suggested to improve prostate-specific antigen (PSA) level, prostate-cancer specific survival and distant metastases-free survival[21]. These results led to consider the association of metformin with docetaxel in mCRPC as a promising strategy.

The TAXOMET study investigated the impact of the addition of metformin to docetaxel chemotherapy on PSA-response in non-diabetic mCRPC patients.

METHODS

Patients

The study enrolled patients age 18 years or older with a mCRPC who had disease progression under androgenic deprivation therapy. Eligible patients had documented histologic diagnosis of prostate adenocarcinoma and a serum testosterone level lower than 50 ng/dL. Disease progression was defined as at least one of the following : an increasing serum level of PSA on three consecutive measurements obtained at least one week apart (with a minimal value of 2ng/mL at the enrollment) or a progression on CT scan according to the modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST 1.1) or a progression on bone scan with appearance of two or more new lesions on bone scan during hormone ablation treatment) according to Prostate Cancer Clinical Trials Working Group 2 (PCWG2)[22]. Patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 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 (except estramustine), diabetes, brain metastases, peripheral neuropathy of grade 3 or higher, and a radiotherapy treatment in the 4 weeks before the enrollment.

Study design

TAXOMET is a randomized, double-blinded, phase 2 study. Patients were recruited in 10 French centers from January 2013 to May 2018. Patients were randomly assigned at a 1:1 ratio to either docetaxel plus metformin (D+M) or docetaxel plus placebo (D+P). Docetaxel 75mg per square meter (m^2) 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 docetaxel on day 1. Antiemetic medication and primary prophylactic granulocyte-colony stimulating factor were prescribed at physician's discretion. Metformin or placebo was administered orally at 850mg twice daily, as previously described[23], except for 48 hours after having a CT scan with iodinated contrast agent. Up to 10 cycles of treatment were planned. Treatment delays of up to 3 weeks and up to one dose reduction were allowed. A docetaxel delay or dose reduction (to 60mg/m2) was specified for patients who had an absolute neutrophil count of less than 1500 per cubic millimeter and for those with grade 3 or 4 thrombocytopenia. A permanent discontinuation was granted for patients who had a grade 4 neutropenia with an oral temperature of at least 38.5°C, a grade 4 thrombocytopenia or a neurotoxicity grade 3. Dose reduction was not allowed for metformin or placebo. Because of drug interaction, furosemide, nifedipine and angiotensin converting enzyme inhibitors were forbidden. Metformin 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. Metformin or placebo was also discontinued in case of docetaxel interruption. Androgen deprivation therapy had to be maintained during the study. All patients provided written informed consent before any screening procedures were initiated. The study was approved by the local ethics committee at each participating site and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Endpoints

The primary end point was the PSA response rate defined by the Prostate Cancer Clinical Trials Working Group (PCWG2) criteria[22]. 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 baseline (PSA-50), confirmed after three weeks, 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. A complete response was defined by a PSA decline under 4ng/mL in absolute value.
Main secondary endpoints were the objective response rate (ORR), the progression-free survival (PFS), overall survival (OS) and safety. PFS was defined as the time from randomization to progression or death, including the time until PSA, radiographic, clinical progression or death of any cause. The ORR was evaluated with computed tomography according to mRECIST v1.1[24] 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 AEs and serious AEs (SAEs), 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 classified according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.
Prespecified exploratory endpoints included quality of life 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

The primary endpoint (PSA-50 response rate) was assessed in the intention-to-treat population. The study assumed that docetaxel + metformin 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 in each group were required to detect an effect on PSA-50 response rate. Assuming that 5% of patients would not be evaluable, the number of patients to include was 50 patients in each group. No interim analysis was planned. Progression-free survival (PFS) and overall survival (OS) were presented using Kaplan-Meier curves, with 5 years of follow up. Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated using Cox model. 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. The quality of life data were analyzed by comparing the global health status mean score between the two treatment arms. Comparisons were made at three separate times: at baseline (before cycle 1), at cycle 6, and at the end of treatment. All analyses were made using the R.3.5.1 software. This study was registered in Clinical Trial.gov, number NCT01796028.

RESULTS

Patients

Between January 2013 and December 2015, 99 non-diabetic patients with mCRPC were enrolled in 10 french sites. 50 patients were assigned to docetaxel plus prednisone and metformin (D+M) and 49 were assigned to docetaxel plus prednisone and placebo (D+P). One patient in the D+P arm withdrew consent and was not included in the analysis **(Figure 1)**. The median follow-up in the overall study population was 41.1 months (95% CI, 38.5 to 54.1 months).

Patient's characteristics are summarized in **Table 1**. The two arms were well balanced, except for 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 with D+M vs 54.5 ng/mL with D+P).

Treatment exposure disposition is summarized in **Supplementary Appendix**. Less than 40% of patients in each arm reached the 10 cycles. The median number of treatment cycles was 7 in both arms. Docetaxel dose reduction were required for 4 (8%) patients in the D+M arm and 7 (15%) in the D+P arm.

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

G-CSF prophylaxis was used for 28% and 24% of patients with D+M and D+P, respectively.

Efficacy

Among the 99 patients, 75 patients died, 69 had a PSA progression, 12 had a radiographic progression (according to RECIST 1.1 criteria) and 3 had a bone scan progression (according to PCWG2 criteria).

The PSA-50 response rate (primary endpoint) was similar across treatment arms: 66% in the D+M arm (47 evaluable patients) and 63% in the D+P arm (48 evaluable patients) **(Figure 2)**

Median time to PSA progression was 8.5 months in the D+M arm (95% CI 7.3-10.1) and 8.9 months in the D+P arm (95% CI 6.0-10.5), HR 0.96 (95% CI 0.64-1.44); p=0.85.

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

A total of 95 PFS events occurred in the ITT population: 96% in the D+M arm and 96% in the D+P arm. Median PFS was 7.8 months (95% CI 5.1-9.6) in the D+M arm and 6.0 months (95% CI 4.8-9.1) in the D+P arm (HR 1.08, 95% CI 0.72-1.62; p=0.70) **(Figure 3A)**.

A total of 75 OS events occurred in the ITT population: 76% in the D+M arm and 76% in the D+P arm. Median OS was 24,6 months (95% CI 18.5-33.7) in the D+M arm and 19,7 months (95% CI 15.7-36.8) in the D+P (HR 1.10, 95% CI 0.69-1.73; p=0.70) **(Figure 3B)**.

The primary reason for death was disease progression (n=68), septic shock (n=2) 14 and 15 months after docetaxel discontinuation, nosocomial infection (n=1), subdural hematoma (n=1), catheter related infection (n=1) 9 months after docetaxel discontinuation, thromboembolic disease (n=1) and suicide (n=1).

Safety

There was no clinically relevant difference in the safety profile between the two arms, except for diarrhea, with an expected increase incidence of all-grade diarrhea with metformin (77% in the D+M arm vs 50% in the D+P arm), but a similar rate of grade 3-4 diarrhea in each arm. Some AEs were more commonly observed in the D+P arm, among which constipation, abdominal pain, vomiting and febrile neutropenia. Conversely, decrease appetite and dysgeusia were more commonly observed in the D+M arm **(Table 2).** 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. Compared with baseline, there was a statistically significant improvement of QoL at cycle 6 for patients in the D+M arm with a median score of 73.7 [33-100] vs 57.8 [8.3-100] (p=0.0035) (**Figure 4**). Indeed D+M population had a better role functioning score (mean score = 85 vs 71, SD = 18 vs 26 respectively) and physical functioning score (mean score = 86 vs 74, SD = 12 vs 20) than the D+P arm. This difference was not observed at the end of the treatment.

Discussion

Docetaxel was shown to be the first known agent to extend survival in patients with mCRPC. New survival-prolonging therapies have been approved before or after this chemotherapy setting. Optimization of docetaxel treatment has been investigated. However, among all docetaxel-based combination studies, no one reported to date showed to extend survival compared to docetaxel alone[25]. In the past few years, the controversial reported results of the effect of metformin on the incidence and prognosis of PCa has been increasing. Metformin exhibits its own advantages in PCa cell cycle progression and androgen-dependent transcription by reducing cyclin D1 expression[26]. These data have raised the question of the potential benefit of metformin-based treatment to improve outcome in PCa, with a suggested favorable toxicity profile.

TAXOMET is the first prospective randomized controlled study reporting the effect of the addition of metformin to standard first-line docetaxel and prednisone chemotherapy in mCRPC population compared with docetaxel plus placebo. The characteristics of the patients in the present study were comparable to the previous reported docetaxel-based trials in this setting TAX327[4] and SWOG-99-16[5]. The median number of cycles (7) and the median overall survival also compared favorably to those classically observed. In the TAXOMET study, some characteristics were not strictly comparable in both arms, as the patients in the D+M arm had a higher Gleason score and a higher median PSA level at baseline than in the D+P arm. With these limitations, the study results did not point out any significant benefit of metformin either in PSA response, PFS or OS, when combined to docetaxel. However, as metformin was discontinued at the same time with docetaxel, after a maximum of 10 cycles, the study design did not provide information about the role of metformin in maintenance after the end of docetaxel. The safety profile of metformin was consistent with that was expected, providing more diarrhea grade 1 or 2 in the D+M arm. AE of grade 3 or higher was similar between the two arms. Moreover, no degradation of QoL was observed in both arms. QLQ-C30 score at the 6th cycle was statistically better in the D+M than in the D+P arm, with the limitation that more patients had received up to 6 cycles in the D+M arm (36 vs 29) and might represent a more fit population.

Since the early 2000s, *in vitro* studies showed that metformin might influence cancer cell proliferation and induce apoptosis[27]. Its anti-cancer effect exerts via two mechanisms: directly (insulin-independent) via inhibition of the mitochondrial electron transport chain[13] and subsequent reduction of ATP concentration leading to an energy stress[28] but also indirectly (insulin-dependent), via inhibition of hepatic gluconeogenesis[29] resulting in a decrease of insulin secretion. Reducing circulating insulin leads to a sub-sequent down-regulation of the Phosphoinositide 3-kinase (PI3K) axis, which is involved in cancer proliferation. In a preclinical study, hyperglycemia reduced docetaxel-induced death in androgen-independent cell lineages. Conversely, co-treatment with metformin and docetaxel was effective to increase cell death in both normo- and hyperglycemia condition[30]. However, there are possible explanations for the lack of clinical effect of metformin in non-diabetic patients. Insulin could increase intratumoral androgen production in PCa[31] but the optimal regulation of circulating insulin could explain the lack of impact of metformin. Some retrospective and meta-analysis data suggested that the survival benefit with metformin could be preferentially observed in diabetic metformin users compared to diabetic non-metformin users as well as non-diabetic patients[21,32].

In a retrospective study, Mayer et al. reported that the combination of metformin with docetaxel did not seem to affect castration resistant PCa-specific survival and overall survival in diabetic patients[33]. In a single arm-phase 2 study, the addition of metformin to the AR-targeting therapy abiraterone in non-diabetic patients with metastatic CRPC and PSA progression while receiving abiraterone did not affect further progression and did not seem either to have a meaningful clinical benefit[34]. Then, a recent meta-analysis suggested that the addition of ADT with metformin improved PCa-specific survival and overall survival, which could suggest a greater sensitivity to metformin in castration-sensitive prostate cancer population[35].

More than 50% of men who received long-term ADT classically develop a metabolic syndrome[36], which is an important factor for biochemical failure after prostatectomy and radiotherapy. Metformin exhibited therapeutic benefits for weight gain induced by insulin resistance[35]. Best supportive care to mitigate the current adverse metabolic effects of prolonged ADT, including metabolic dysfunction, insulin resistance, hyperglycemia and obesity, is a milestone in the management of patients with a PCa. Through a potential improvement in quality of life and the treatment of diabetes associated with metabolic syndrome, metformin may represent an important actor of multimodal strategy for PCa patient treated with ADT.

More than 10 studies investigating the role of metformin alone or in combination with other systemic treatments and/or radiation therapy are ongoing in localized or advanced PCa. Among them, we are looking forward to the STAMPEDE trial results, which investigate the role of metformin associated to standard of care in locally advanced or metastatic PCa.

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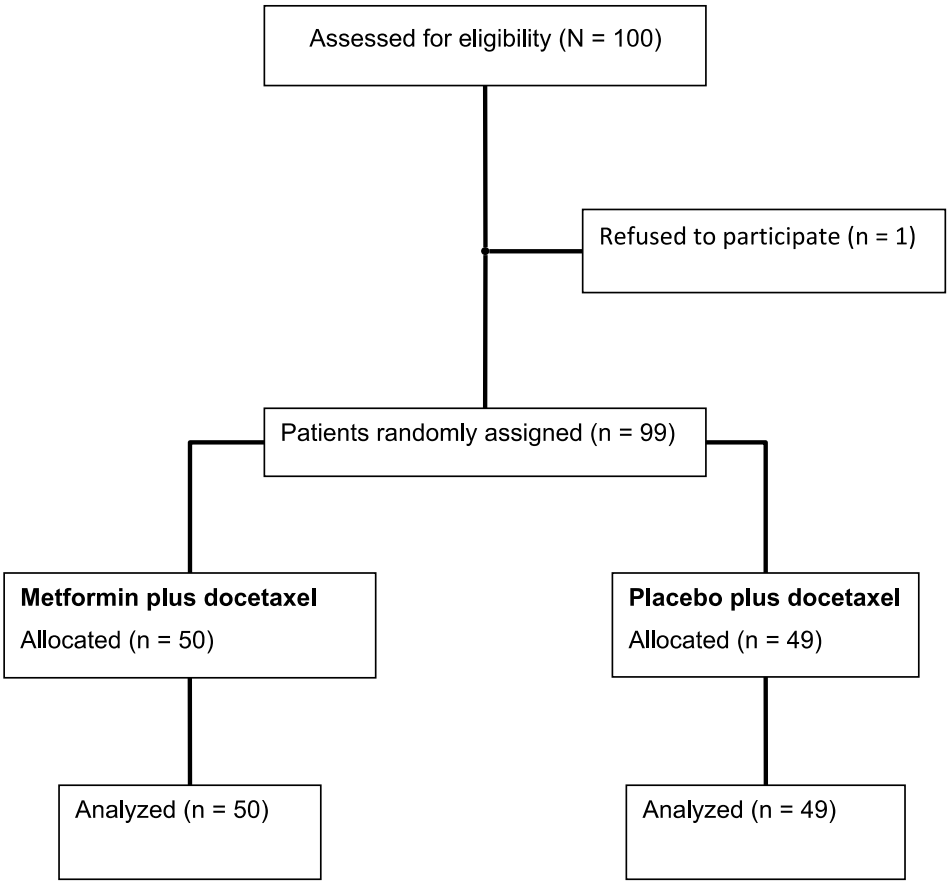

Figure 1 – TAXOMET CONSORT Diagram

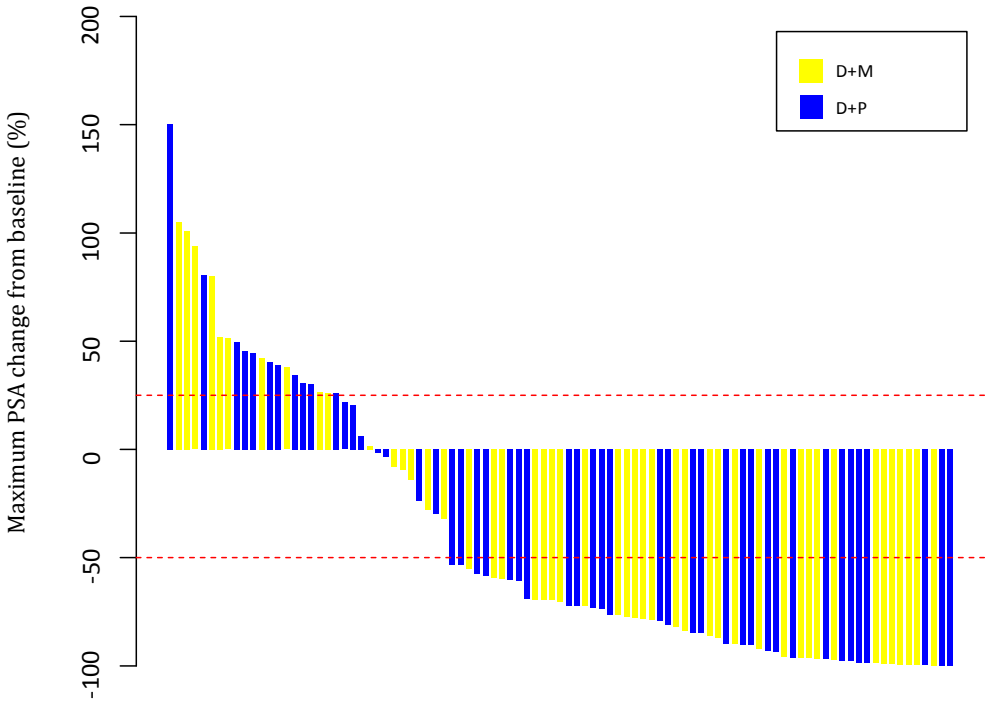

Figure 2 – Waterfall plot for best PSA response
D+M : Docetaxel + Metformin
D+P : Docetaxel + Placebo

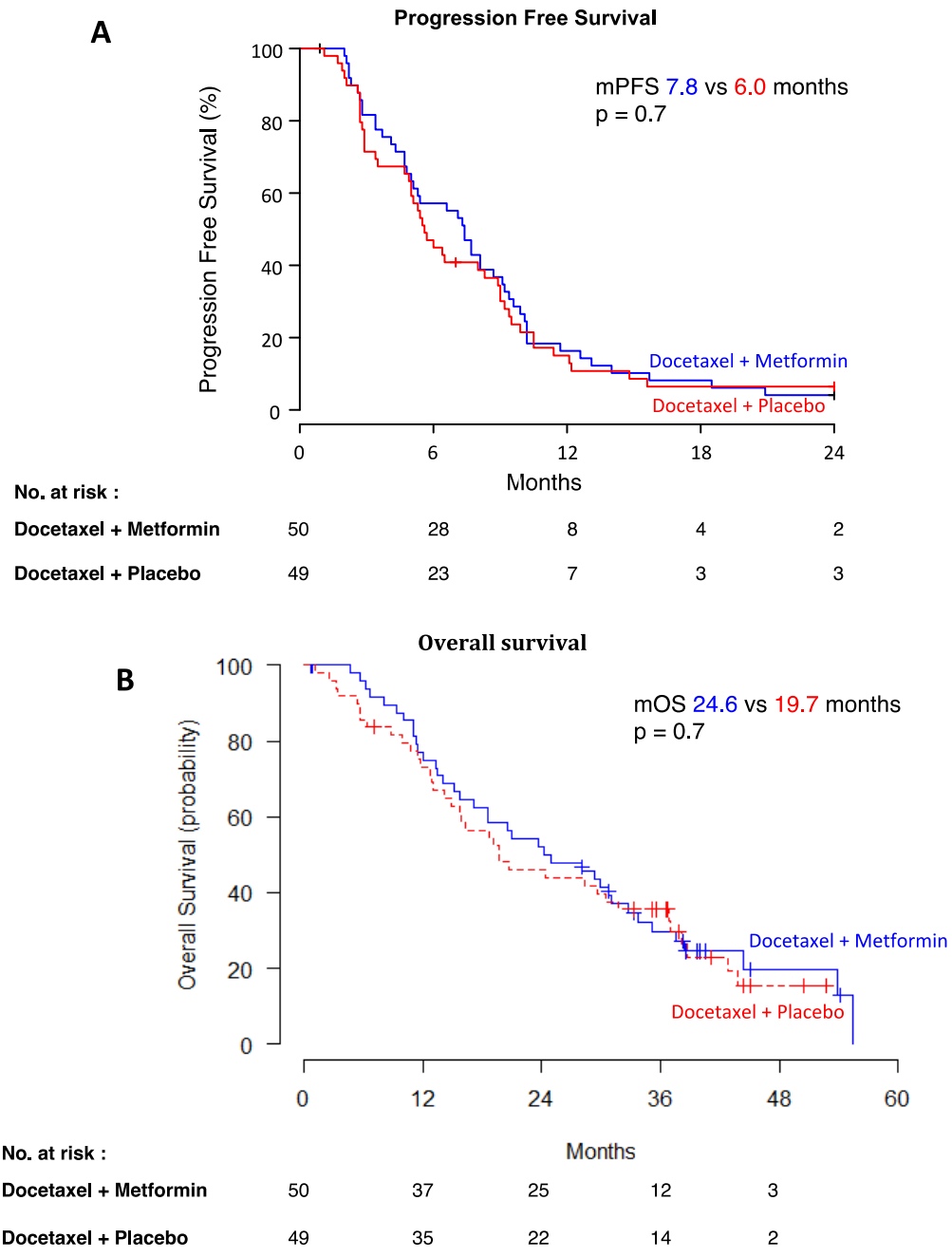

Figure 3 – Kaplan Meier estimates of progression free-survival (A) and overall survival (B)

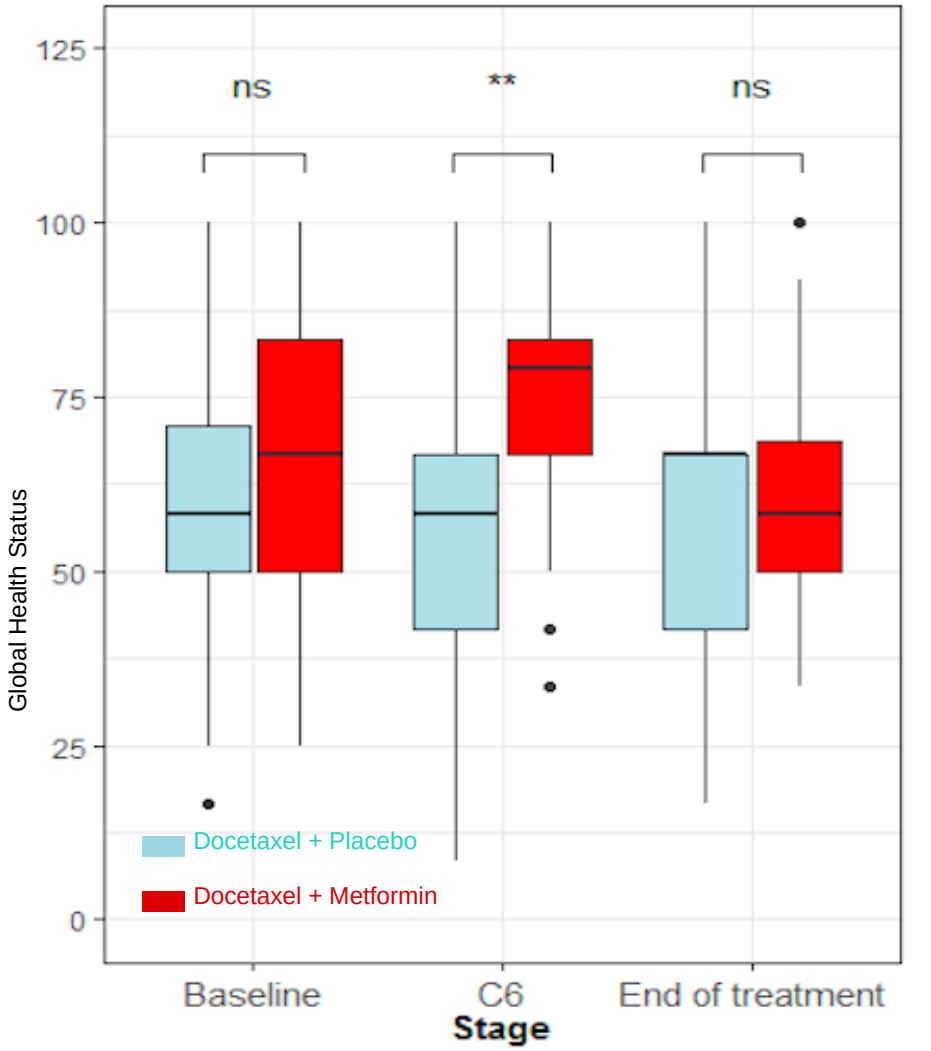

Figure 4 – QoL: Boxplot of the QLQ-C30 questionnaire at baseline, at cycle 6 and at the end of the treatment
**: statistically significant $p < 0.01$

	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 1 2	 25 (50) 24 (48) 1 (2)	 17 (35) 28 (57) 4 (8)
Gleason Score, n (%) 6 7 ≥ 8 Unknown	 6 (12) 13 (26) 30 (60) 1 (2)	 8 (16) 16 (33) 23 (47) 2 (4)
Site of metastases, n (%) Lymph node Bone Visceral *Lung* *Liver* Others	 26 (52) 36 (72) 12 (24) 7 (14) 5 (10) 1 (2)	 25 (51) 37 (76) 11 (22) 7 (14) 4 (8) 1 (2)
Number of previous hormonal therapies, n (%) 1 2 ≥ 3	 18 (36) 23 (46) 9 (18)	 14 (29) 20 (41) 15 (30)
Previous Abi or Enza, n (%) Abiraterone acetate Enzalutamide Others	 9 (18) 1 (2) 1 (2)	 9 (18) 0 (0) 2 (4)
Median baseline PSA, ng/mL [range]	80.3 [5.1-11,4]	54.5 [2.5-3,3]
Median Time to progression to CRPC	7.20 [0.50-60.60]	10.30 [0.30-131.40]

Table 1- Baselines characteristics (intention to treat population)
IQR : interquartile range

Adverse event	Docetaxel+Metformin (N = 50)		Docetaxel+Placebo (N = 49)	
	Any Grade, n (%)	Grade 3-4, n (%)	Any Grade, n (%)	Grade 3-4, n (%)
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)

Table 2 – Summary of Frequently-Reported AEs Occurring in ≥ 5% of patients in either treatment group (safety analysis set)

	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][§]	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 investigation decision	1 (<1)	0
Others	6 (12)	4 (8)

Supp. - Treatment exposure

G-CSF: granulocyte stimulating factor

[§]The ratio of metformin or placebo dose delivered rate to metformin or placebo dose planned during the treatment.

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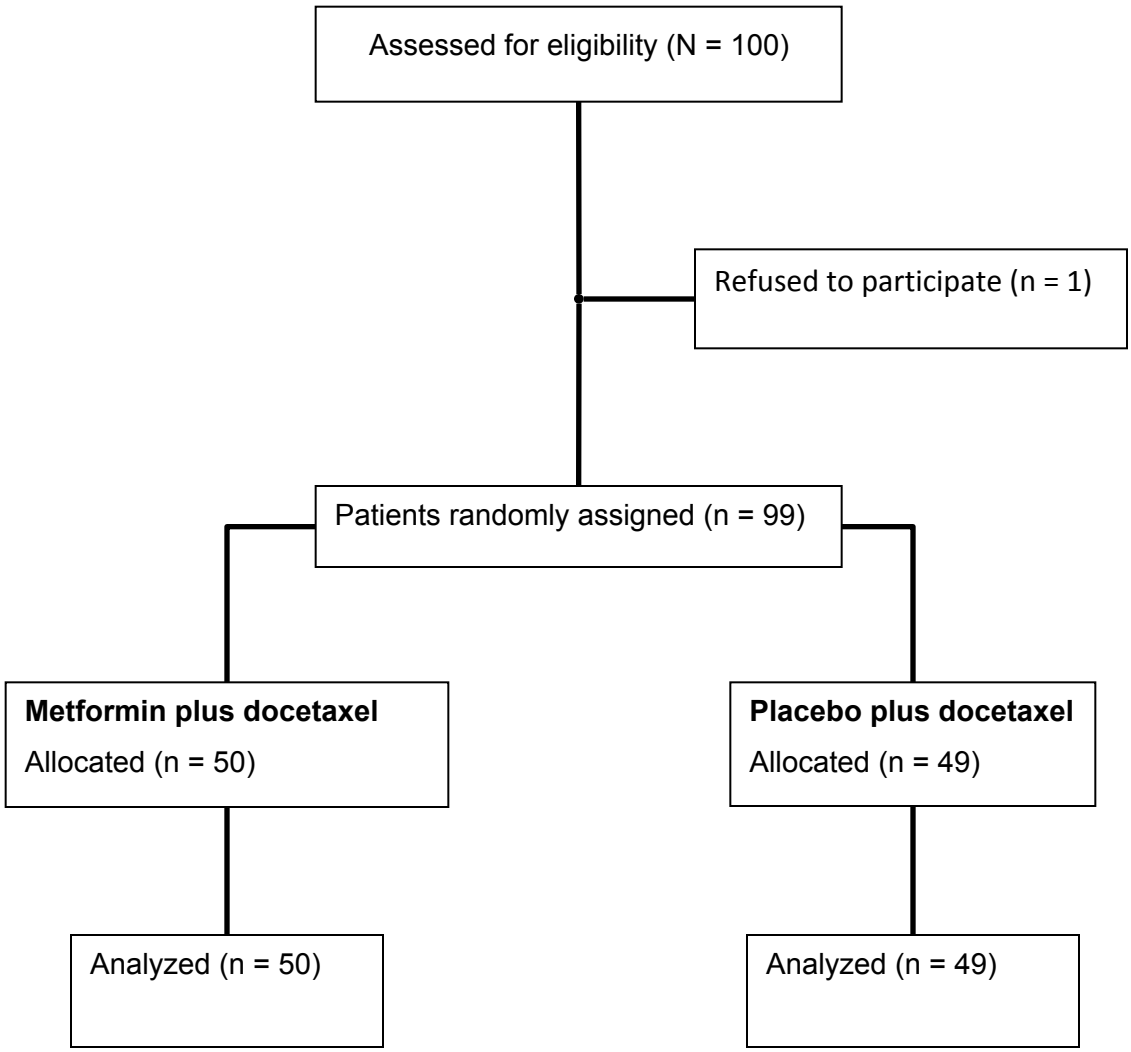

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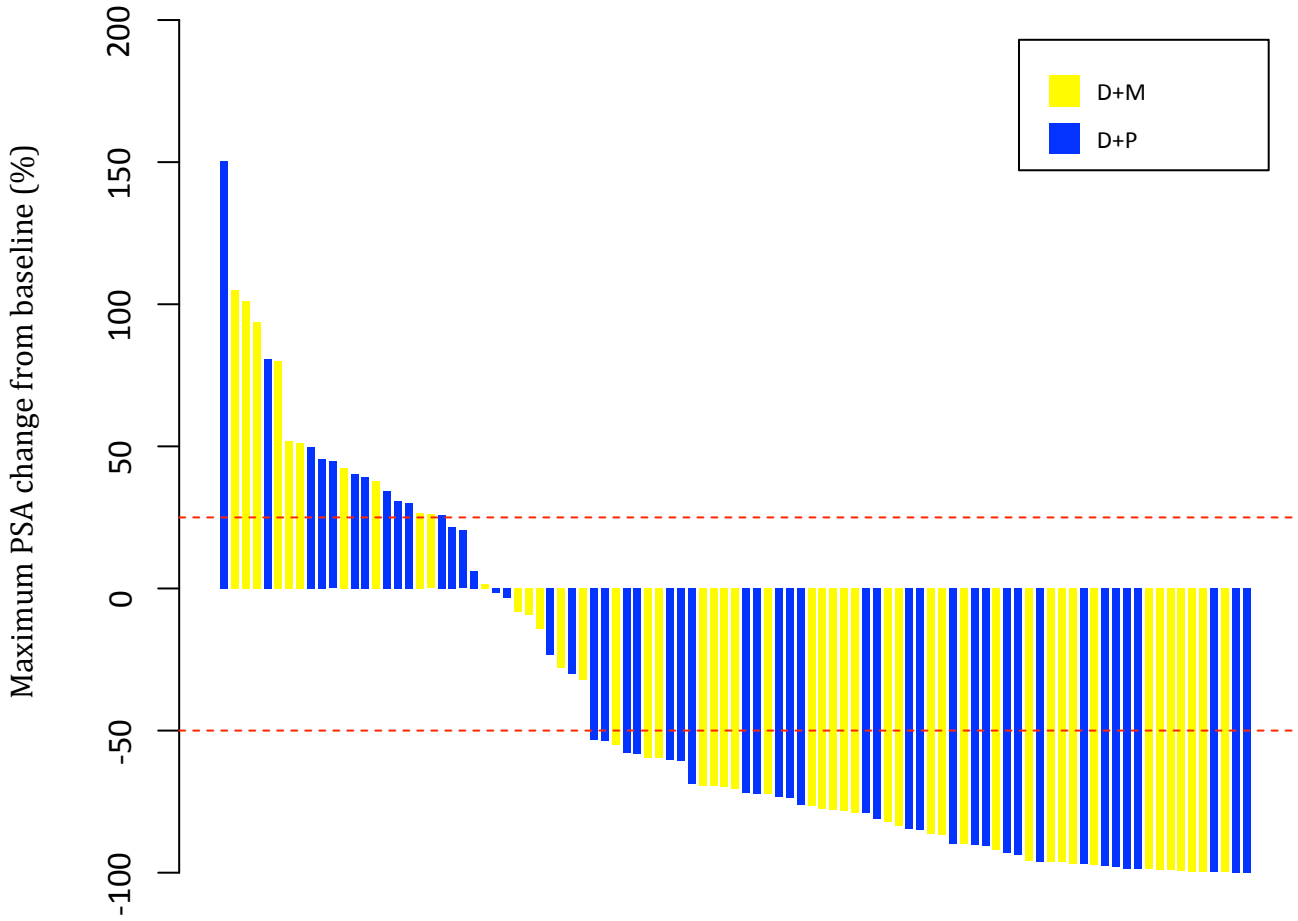

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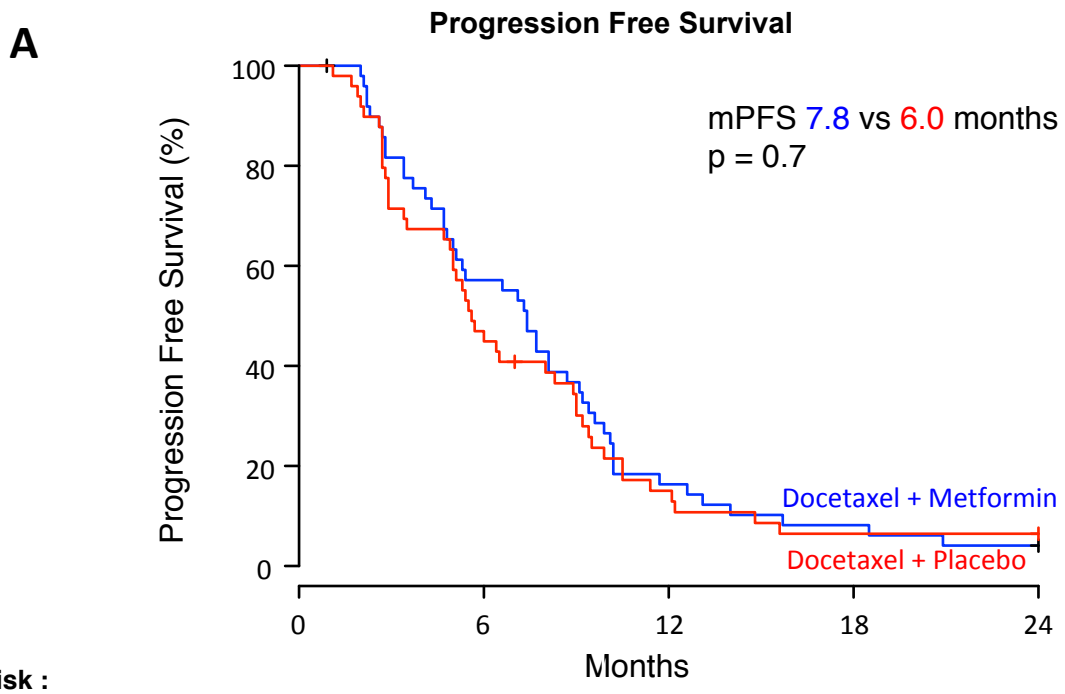
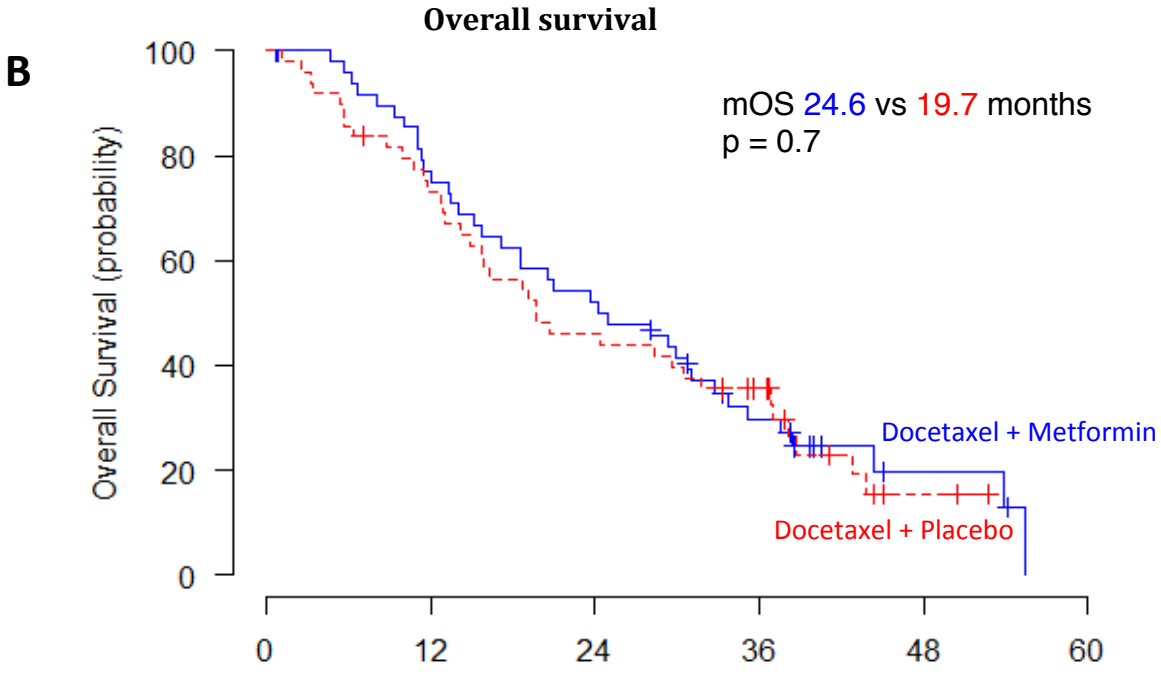


No. at risk :					
Docetaxel + Metformin	50	28	8	4	2
Docetaxel + Placebo	49	23	7	3	3



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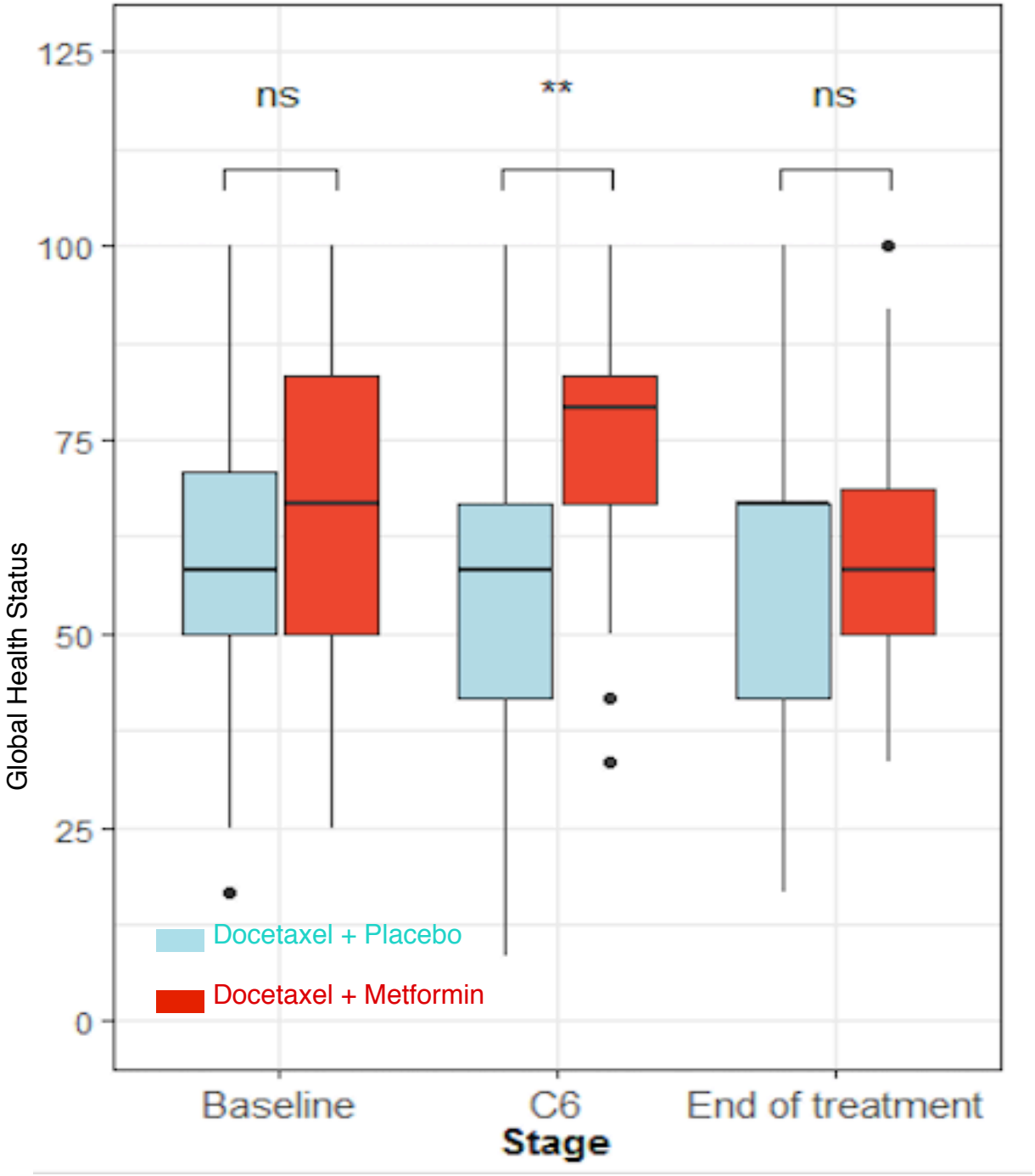

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2	1 (2)	4 (8)
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≥ 8	30 (60)	23 (47)
Unknown	1 (2)	2 (4)
Site of metastases, n (%)		
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Bone	36 (72)	37 (76)
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