Metformin in Chemotherapy-naive Castration-resistant Prostate Cancer: A Multicenter Phase 2 Trial (SAKK 08/09)

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Abstract

Background: There is evidence linking metformin to improved prostate cancer (PCa)-related outcomes.
Objective: To evaluate treatment with metformin in patients with castration-resistant PCa (CRPC) and the effect of the treatment on progression-free survival (PFS) and PSA doubling time (PSA DT).
Design, setting, and participants: Forty-four men with progressive metastatic CRPC from 10 Swiss centers were included in this single-arm phase 2 trial between December 2010 and December 2011.
Intervention: Patients received metformin 1000 mg twice daily until disease progression.
Outcome measurements and statistical analysis: The primary end point was the absence of disease progression at 12 wk. Simon two-stage optimal design was applied. With a 5% significance level and 90% power, 44 patients were required to test PFS at 12 wk $\leq$15% (H_0) compared with $\geq$35% (H_1).
Results and limitations: Thirty-six percent of patients were progression-free at 12 wk, 9.1% were progression-free at 24 wk, and in two patients a confirmed $\geq$50% prostate-specific antigen (PSA) decline was demonstrated. In 23 patients (52.3%) we observed a prolongation of PSA DT after starting metformin. The homeostatic model assessment index fell by 26% from baseline to 12 wk, indicating an improvement in insulin sensitivity. There was a significant change in insulin-like growth factor-1 and insulin-like growth factor binding protein 3 from baseline to 12 wk. Sample size and lack of a control arm are the limitations of this trial; analyses are therefore exploratory.
Conclusions: Treatment with metformin is safe in nondiabetic patients, and it yields objective PSA responses and may induce disease stabilization. The activity of metformin in PCa, along with its low cost, favorable toxicity profile, and positive effect on metabolic parameters, suggests that further investigation of metformin as therapy for patients with PCa is of interest.
Patient summary: In this trial we assessed the use of the diabetes mellitus drug metformin in patients with advanced prostate cancer. We found disease stabilization and prolongation of prostate-specific antigen doubling time in some patients as well as effects on metabolic parameters.
Trial registration: This study is registered with ClinicalTrials.gov with the identifier NCT01243385.

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1. Introduction

Men undergoing androgen-deprivation therapy (ADT) for advanced or metastatic prostate cancer (PCa) are at risk for developing insulin resistance, hyperglycemia, and obesity [1–3]. High C-peptide levels and high body weight in men with a subsequent PCa diagnosis are independent predictors of increased PCa-specific mortality (PCSM) [4]. Metabolic syndrome is associated with a shorter time to prostate-specific antigen (PSA) progression and shorter overall survival (OS) in patients receiving ADT [5].

The biguanide metformin is an inexpensive, well-known oral drug used in the treatment of diabetes mellitus. Metformin has antiproliferative effects in preclinical models of PCa via reduction of systemic insulin levels and inhibition of mammalian target of rapamycin (mTOR) [6–8]. In a recent population-based evaluation among 3837 diabetic patients with PCa, metformin use was associated with reduced PCSM and reduced all-cause mortality [9]. Several studies have shown metformin to be safe in patients without diabetes mellitus, and no episodes of hypoglycemia were reported [10–13].

This phase 2 trial conducted by the Swiss Group for Clinical Cancer Research investigates the activity of metformin as first-line treatment in patients with progressive castration-resistant PCa (CRPC) and the effects of metformin on metabolic parameters. Our hypothesis was that ≥35% of patients would be nonprogressing after 12 wk of treatment. A set of blood-derived PI3K/Akt pathway–sensitive protein biomarkers [14] was analyzed for prediction of reaching the primary end point.

2. Materials and methods

2.1. Patient eligibility

Eligibility criteria included adenocarcinoma of the prostate confirmed by central pathology review, metastatic or locally advanced disease, progression on ADT, castration-level testosterone ≤50 ng/dl, no prior chemotherapy, no diabetes mellitus, and no prior use of metformin or other diabetes mellitus treatment. PSA progression was defined as an increase in PSA ≥25% (absolute increase ≥2 ng/ml) above nadir on hormonal therapy measured on three successive occasions ≥1 wk apart. Patients had to be oligosymptomatic or asymptomatic, with a World Health Organization performance status of 0–1. The following values were required: PSA <114 ng/ml, PSA doubling time (PSA DT) ≥55 d, and adequate organ function.

All patients signed informed consent forms. The trial was approved by the ethics committee, was registered (NCT01243385), and followed the current Guideline for Good Clinical Practice issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [15] and the Declaration of Helsinki.

2.2. Trial design and treatment

This single-arm phase 2 trial evaluated treatment with metformin in patients with CRPC and confirmed disease progression. ADT was continued in nonsurgically castrated patients. Metformin was administered continuously at 1000 mg twice daily in uninterrupted 4-wk cycles. The metformin dose was increased stepwise (500-mg steps) within 2 wk to the target dose. Treatment was continued until progression, unacceptable toxicity, or refusal.

2.3. Trial evaluations (response evaluation and toxicity)

2.3.1. Assessments

Physical condition, safety, and drug-related toxicities were evaluated on scheduled visits every 4 wk during trial treatment. Adverse events (AEs) were defined by National Cancer Institute Common Terminology Criteria for Adverse Events v.4.0 [16]. Disease status was assessed every 12 wk with physical examination; computed tomography of the chest, abdomen, and pelvis; bone scanning; PSA; and laboratory evaluation in accordance with the Prostate Cancer Clinical Trials Working Group recommendations [17].

Metabolic parameters were assessed at baseline: body mass index (BMI), glycosylated hemoglobin (HbA1c), fasting glucose, insulin, and C-peptide. The homeostatic model assessment (HOMA) index was determined (insulin [μU/ml] × glucose [mmol/l] / 22.5), with values ≥2 indicating insulin resistance [18].

In a subset of patients, a glucose tolerance test was performed before the start of metformin and after 12 wk. Serum specimens were analyzed for glucose, insulin, C-peptide, insulin-like growth factor-1 (IGF-1), and insulin- like growth factor binding protein 3 (IGFBP3) before and after a 75-g glucose load.

2.3.2. Serum biomarkers

Metformin inhibits the PI3K pathway by way of activation of adenosine monophosphate–activated protein kinase. Hence, we tested PI3K/Akt–sensitive blood-based proteins for their potential use as predictive biomarkers. Originally, 49 candidate protein biomarkers were identified by a genetic-guided discovery approach using mass spectrometry and were shown to mirror PI3K/Akt activity in localized PCa [14]. Recently, these proteins were further tested in patients with CRPC receiving the mTOR inhibitor everolimus. Twelve proteins were predictive for reaching the primary end point, progression-free survival (PFS) at 12 wk (PFS12) [19]. For these 12 candidate biomarkers, seven enzyme-linked immunosorbent assays were commercially available and tested in this trial before the start of metformin and after 12 wk.

2.3.3. Statistical considerations

The primary end point, PFS12, was binary, defined as absence of progression (PSA increase ≥25% above baseline, progression of measurable disease or bone lesions, clinical progression, start of palliative radiotherapy) or death at week 12 (±1 wk). Patients without assessment in this time period were counted as progressive unless they had a positive outcome measured at a later date.

Simon two-stage optimal design was applied. No good published references were available, so the thresholds of 15% and 35% were chosen, as they were considered clinically meaningful considering that metformin is inexpensive and usually well tolerated. With a one-sided 5% significance level and 90% power, 44 evaluable patients were required to test PFS12 ≤15% (H_0) compared with ≥35% (H_1). At the interim analysis after 19 patients reached week 12, the trial would have been stopped if ≤3 of the 19 patients had been PFS12. If ≥11 evaluable patients remained PFS12 by the end of the trial, the trial treatment would be deemed worthy of further investigation.

Secondary end points were PFS at 24 wk (PFS24); PFS; clinical benefit rate at 12 wk and 24 wk, defined as response or stable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) and clinically stable; PSA response (50% and 30% maintained for ≥3 wk, best, and at 12 wk); changes in PSA DT; response of measurable disease according to RECIST v.1.1; assessment of bone lesions; OS; and toxicity.

The secondary end points PFS and OS were calculated from treatment start until the event of interest and analyzed using the Kaplan-Meier method. PSA DT was calculated from the natural log of 2 divided by the slope of the relationship between the log of PSA and the time of PSA measurement. For continuous variables, independent groups were compared using Wilcoxon rank sum tests, and paired measurements were compared using Wilcoxon signed rank tests. Logistic regression models were used to test the effect of metabolic parameters on PFS12, PSA decline, and PSA progression. The association of serum biomarkers with PFS was tested using univariate Cox models. To obtain more interpretable results, the values were normalized by their interquartile range (IQR). All tests for secondary end points and translational research were two-sided, with a 5% significance level. As no adjustment for multiple testing was applied for analyses other than the primary end point analysis, they were exploratory and hypothesis generating. All analyses were performed using SAS v.9.2 (SAS Institute, Cary, NC, USA) and R v.2.15.2 (http://www.r-project.org).

3. Results

3.1. Patient characteristics

Forty-four patients were enrolled at 10 Swiss centers between December 2010 and December 2011. Baseline demographic and disease characteristics are listed in Table 1. In total, 206 cycles of metformin were administered, with a median of 3.5 (IQR: 3.0–6.0) cycles.

Table 1 – Baseline characteristics

Overall (n = 44)		
Variable	Median	Q1,Q3
Age, yr	70	63,78
Height, cm	174	170,179
Weight, kg	86	78,94
BMI, kg/m^2	27.8	25.2,31.9
Serum creatinine, μmol/l	74	68,88
Calculated creatinine clearance, ml/min	88	74,111
Glucose, mmol/l (n = 43)	5.6	5.2,6.4
HbA1c, mmol/l (n = 35)	6.0	6.0,6.0
Serum PSA, μg/l	29	17,59
PSA doubling time, d	88	65,152
Variable	**No.**	**%**
Gleason score at diagnosis		
Unknown	6	14
6	2	5
7	11	25
8–10	25	57
WHO performance score		
0	31	71
1	13	30
Extent of disease		
Bone metastases	28	64
Lymph node metastases	19	43
Liver metastases	2	5
Other metastases	10	23
Previous treatment		
LHRH	37	84
Orchiectomy	7	16
Tumor surgery		
Prostatectomy	18	41
TURP	12	27
Radiotherapy/brachytherapy		
Yes	17	39
Hormonal therapy other than LHRH		
Bicalutamide	34	77

BMI = body mass index; PSA = prostate-specific antigen; WHO = World Health Organization; LHRH = luteinizing hormone–releasing hormone; TURP = transurethral resection of the prostate.

3.2. Efficacy

At the end of the trial, 16 patients (36%; 95% confidence interval [CI], 22–52) were progression-free at week 12. Reasons for progression at week 12 were PSA progression only in 19 patients (43%), clinical progression in 2 patients (5%), and progression according to RECIST in 2 patients (5%). Five patients (11%) stopped treatment before 12 wk and were classified as progressive disease (PD).

Four patients (9%; 95% CI, 3–22) were progression-free at week 24. The median PFS was 2.8 mo (95% CI, 2.8–3.2). Two patients (5%; 95% CI, 1–16) have shown a confirmed ≥50% maximal PSA decline (Fig. 1). One patient obtained a partial response according to RECIST on computed tomography; this patient also had a confirmed ≥50% PSA decline. The median PSA DT from baseline to week 12 (or treatment stop) was 111 d (IQR: 45–197), compared with a median PSA DT prior to treatment start of 88 d (IQR: 65–152) (Fig. 2). In 23 patients (52%), we observed prolongation of PSA DT after initiation of metformin treatment; however, this change in PSA DT was not significant (p = 0.7).

Twenty patients (46%) were deemed to derive clinical benefit from metformin after 12 wk. Fourteen patients (32%) continued treatment for >24 wk; the median time on treatment was 13.6 wk (IQR: 11.9–24.4). With a median follow-up of 16.9 mo (IQR: 12.3–20.1), three patients (7%) have died.

3.3. Safety

Treatment-related AEs were mild and manageable. Eight patients (18%) experienced a total of nine serious AEs, six considered unrelated and three unlikely related to treatment. No related grade 3 or 4 AEs occurred during the treatment period. There were no episodes of lactic acidosis or hypoglycemia (Table 2).

3.4. Metabolic analyses

The median BMI at baseline was 27.8 kg/m^2 (IQR: 25.2–31.9); 21 patients (48%) had a BMI of 25–29.9 kg/m^2, indicating overweight; and 13 patients (30%) had a BMI ≥30 kg/m^2, indicating obesity. The median baseline HbA1c was 6% (IQR: 6–6; normal: <6.5%). The baseline fasting glucose was 5.6 mmol/l (IQR: 5.2–6.4; normal: 3.9–5.6), and the baseline insulin was 8.6 mU/l (IQR: 7.0–11.0). The median HOMA index at baseline was 2.2 (IQR: 1.8–3.5). Eighteen of 32 patients (56%) had a HOMA index >2, suggestive of insulin resistance. The HOMA index fell by 26% from baseline to 12 wk, indicating improvement in insulin sensitivity (Table 3). In 27 and 23 patients, preglucose samples at baseline and week 12, respectively, were

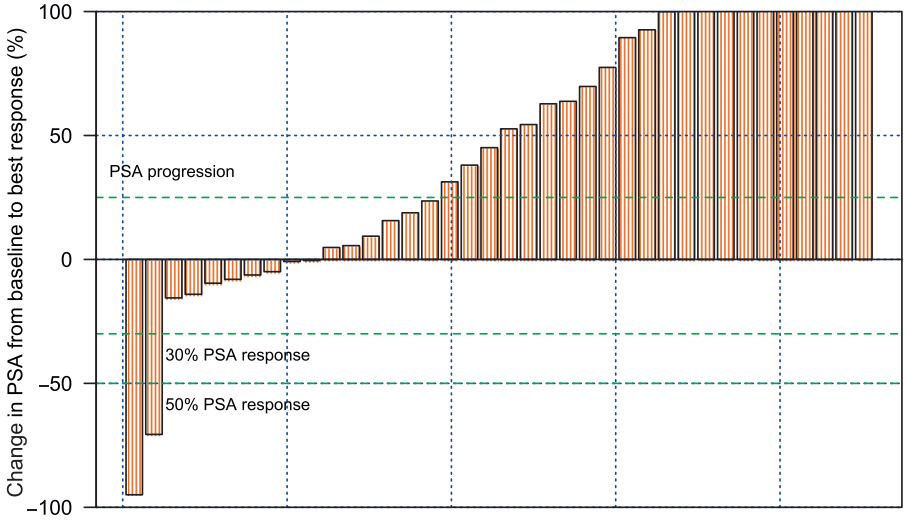

Fig. 1 – PSA response – waterfall plot. PSA = prostate-specific antigen.

available; in 12 patients, postglucose samples at both time points were available. A trend toward decrease in insulin levels before glucose load from baseline to 12 wk was observed (−1.1 mU/l; IQR: −2.9 to 0.4; $p = 0.08$); the change in glucose levels was not significant (−0.2 mmol/l; IQR: −0.6 to 0.4); $p = 0.5$). C-peptide levels did not change over time when assessed before and after glucose.

There was a significant change in IGF-1 or IGBP3 from baseline to 12 wk (Table 4). No significant association was found between changes in metabolic measures and effects on PCa progression in this limited number of samples.

3.5. *Serum biomarkers*

Serum from 37 patients was available for analysis. None of seven candidate biomarkers was significantly associated with reaching the primary end point (Supplemental Table 1). However, the proteins galectin-3-binding protein (LGALS3BP) and complement factor H (CFH) showed a trend, as shown in Figure 3. While LGALS3BP concentration was higher in patients reaching the primary end point, CFH concentration was lower.

Looking at PFS, again, none of the candidate proteins was significantly associated in univariate analysis. There was only weak evidence that higher serum levels of LGALS3BP were associated with longer PFS (IQR-normalized hazard ratio: 0.8; 95% CI, 0.6–1.1; $p = 0.1$) (Supplemental Table 2).

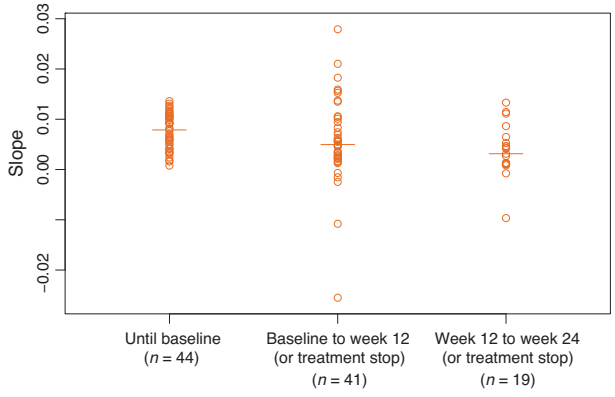

Fig. 2 – Scatter plots and medians of prostate-specific antigen doubling time (PSA DT). PSA DT is calculated from the natural log of 2 divided by the slope of the relationship between the log of prostate-specific antigen (PSA) and the time of PSA measurement.

Table 2 – Adverse events: Clinical adverse events with relation to treatment, all laboratory adverse events

Category	CTCAE term	G1	G2	G3	G4	All grades	%
Clinical	Diarrhea	8	2			10	23
	Fatigue	6	2			8	18
	Nausea/vomiting	6	1			7	16
	Anorexia/weight loss	3	3			6	14
	Pain	1	1			2	5
	Constipation	2				2	5
	Dysgeusia		1			1	2
	Gastritis		1			1	2
	Hypertension		1			1	2
	Bloating	1				1	2
	Dizziness	1				1	2
	Edema	1				1	2
	Flatulence	1				1	2
	Hot flashes	1				1	2
	Urinary incontinence	1				1	2
Laboratory	Anemia	24				24	55
	Raised creatinine	4	1			5	11
	Neutropenia		2			2	5
	Thrombocytopenia	2				2	5
	Hyperbilirubinemia	1				1	2

CTCAE = Common Terminology Criteria for Adverse Events; G = highest grade per patient during treatment.

Table 3 – Homeostatic model assessment calculated using fasting glucose and fasting insulin

Overall (n = 44)				
Variable	No.	Median (95% CI)	Q1,Q3	p value*
HOMA at baseline	32	2.2	1.8,3.5	
HOMA at week 12	23	1.7	1.1,2.4	
Change in HOMA baseline to week 12	23	−0.5 (−1.3 to 0.6)	−1.5,1.6	0.4
% change in HOMA baseline to week 12	23	−25.9 (−41.7 to 47.0)	−52.3,73.0	0.6

CI = confidence interval; HOMA = homeostatic model assessment.
* p values from the Wilcoxon signed rank test.

4. Discussion

To our knowledge, this is the first prospective clinical trial reporting on treatment with the biguanide metformin in patients with progressive CRPC. Sixteen patients (36%) were progression-free at 12 wk, and the median PFS was 2.8 mo. The primary end point of the trial was therefore met. Metformin shows modest activity; however, two patients achieved an objective response with a PSA decline ≥50%, one of them with a partial response of an abdominal wall metastasis. Some patients had stabilization of disease; in others, the PSA dynamic was decelerated with a prolongation of PSA DT.

We planned and performed this trial before randomized data on the efficacy of abiraterone acetate in chemotherapy-naive patients with metastatic CPRC (mCPRC) became available [20]. This setting provided a window of opportunity for proof-of-principle studies to explore novel agents. It is important to note that the safety profile and the costs of metformin are clearly favorable in comparison with other novel agents.

One of the limitations of our trial is the lack of a control arm to compare the treatment effect of metformin with the natural course of the disease. Four patients with a PSA DT of >261 d at baseline were evaluated at 12 wk as not PD. The primary end point of PFS12 could have been met without intervention in these patients. However, one of these patients obtained a PSA response ≥50%.

In 23 patients, we observed prolongation of PSA DT after initiation of metformin. PSA kinetics may represent an intermediate end point in patients with PSA-recurrent PCa treated with nonhormonal agents, as shown in a retrospective post hoc analysis [21]. Changes in PSA DT have also been discussed to indicate disease activity in mCRPC [22].

Measures of hyperinsulinemia are associated with worse cancer outcome, and IGF-1 levels influence cancer risk and prognosis [4,23–25]. Control of the biologic activity of insulin-like growth factor (IGF) is provided by insulin-like growth factor binding proteins (IGFBPs) [26]. Free IGFBPs have antiproliferative activity independent of their IGF-binding capacity [27]. IGFBP3 has antiproliferative and proapoptotic effects in human breast cancer cells in vitro. However, clinical studies suggest that high levels of IGFBP3 in breast cancer tissue are associated with large, highly proliferative tumors [28].

Table 4 – Changes in IGF-1 and IGFBP-3 before and after glucose load

Overall (n = 27)				
Variable	No.	Median (95% CI)	Q1,Q3	p value*
IGF-1 cycle 1 before glucose	27	125.5	79.5,158.3	
IGF-1 cycle 4 before glucose	23	100.9	67.8,137.1	
Change in IGF-1 cycle 1 to 4 before glucose	23	−13.8 (−22.5 to −5.7)	−26.8,2.0	0.003
IGF-1 cycle 1 after glucose	12	119.3	74.8,154.6	
IGF-1 cycle 4 after glucose	12	98.0	59.4,127.0	
Change in IGF-1 cycle 1 to 4 after glucose	12	−17.1 (−27.0 to −7.2)	−28.7,−4.3	0.007
IGF-1 cycle 1 before glucose to after glucose	12	5.4 (0.4–8.7)	0.5,7.7	0.03
IGF-1 cycle 4 before glucose to after glucose	12	3.8 (1.3–12.6)	1.3,10.4	0.009
IGFBP3 cycle 1 before glucose	27	3634.5	2993.5,4065.0	
IGFBP3 cycle 4 before glucose	23	3622.0	2712.5,4034.5	
Change in IGFBP3 cycle 1 to 4 before glucose	23	−278.0 (−437.0 to −39.5)	−486.0,124.5	0.02
IGFBP3 cycle 1 after glucose	12	3272.8	2401.0,3999.3	
IGFBP3 cycle 4 after glucose	12	3480.0	2111.0,3857.0	
Change in IGFBP3 cycle 1 to 4 after glucose	12	−187.3 (−403.5 to 75.0)	−327.0,61.5	0.1
IGFBP3 cycle 1 before glucose to after glucose	12	182.3 (20.8–299.3)	2.0,300.0	0.03
IGFBP3 cycle 4 before glucose to after glucose	12	103.0 (9.8–308.0)	7.5,210.3	0.03

CI = confidence interval; IGF-1 = insulin-like growth factor-1; IGFBP3 = insulin-like growth factor binding protein 3.
* p values from the Wilcoxon signed rank test.

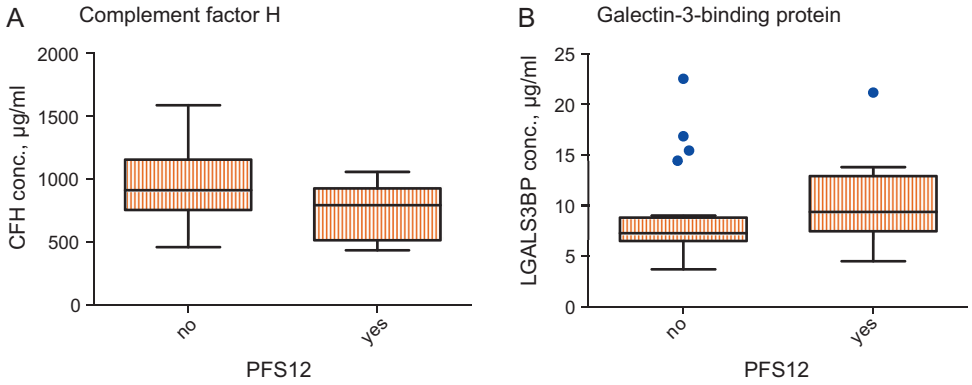

Fig. 3 – Box-and-whisker plots of (A) complement factor H (CFH) levels and (B) galectin-3-binding protein (LGALS3BP) levels illustrate the relation of these proteins to the primary end point, progression-free survival at week 12 (PFS12). conc. = concentration.

Insulin acts directly on PCa cells to increase intratumoral androgen production [29]. Hyperinsulinemia causes activation of IGF-signaling pathways and, subsequently, progression of PCa [30]. Metformin was expected to act by lowering both insulin and IGF levels. However, androgen receptor (AR) signaling may override any inhibitory effects, and there could be mechanisms independent of AR and IGF [31]. Because of the small sample size in the metabolic analyses, the power to find associations between changes in metabolic measures and effects on PCa progression was limited. We observed a decrease in insulin levels after treatment with metformin, while C-peptide levels remained unchanged. Both IGF-1 and IGFBP3 were significantly lower after treatment with metformin when compared with baseline.

The change in the HOMA index was of the same magnitude as in a previous trial with metformin in patients with early breast cancer [10]. An association of fasting insulin levels with outcome in women with early breast cancer was observed in a prospective cohort trial, and high levels of fasting insulin identified women with poor outcomes [23]. This finding led to a phase 3 trial (IBCSG 40–11 MA.32) assessing the effect of adjuvant treatment with metformin for 5 yr on disease relapse [32].

In the protein biomarker analysis, two proteins, LGALS3BP and CFH, showed a trend of association with PFS12, and higher serum levels of LGALS3BP were associated with longer PFS; however, both associations were not significant. We have previously shown that 12 serum biomarkers could predict reaching the primary end point (PFS12) in patients treated with the mTOR inhibitor everolimus in CRPC with an accuracy of $\geq$75% [19]. We postulate that the markers were not significant in the current trial because of an indirect inhibitory effect of metformin on the PI3K-signaling pathway compared with everolimus, which is a direct inhibitor.

The main limitations of the study are the small sample size and missing metabolic and biomarker data, which hampered possible correlation with clinical outcome measures.

5. Conclusions

In summary, our data suggest modest activity of metformin in the treatment of some patients with asymptomatic or minimally symptomatic mCRPC. Both an effect on tumor dynamics and an effect on metabolic parameters may be possible. Metformin is a well-known, well-tolerated, and inexpensive drug and therefore is attractive for use in combination with other anticancer agents, but it cannot be recommended as monotherapy in this setting. Testing metformin in an earlier PCa disease setting and in combinations is of great interest, especially considering the additional effect of metformin on metabolic parameters.

Author contributions: Christian Rothermundt had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cathomas, Gillessen, Pollak, Rothermundt, Templeton.
Acquisition of data: Bärtschi, Cathomas, Endt, Gillessen, Lui, Pollak, Rothermundt, Rüschoff, Schiess, Strebel, Templeton, Winterhalder.
Analysis and interpretation of data: Endt, Gillessen, Hayoz, Rothermundt, Schiess, Templeton.
Drafting of the manuscript: Bärtschi, Cathomas, Endt, Gillessen, Hayoz, Pollak, Rothermundt, Rüschoff, Schiess, Strebel, Templeton, Winterhalder.
Critical revision of the manuscript for important intellectual content: Cathomas, Endt, Gillessen, Hayoz, Rothermundt, Schiess, Templeton.
Statistical analysis: Endt, Hayoz, Schiess.
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Supervision: Gillessen, Cathomas, Rothermundt.
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or patents filed, received, or pending), are the following: Kathrin Endt has been employed in head assay development at ProteoMediX. Silke Gillessen has been on advisory boards at Bayer, Curevac, Janssen Cilag, Millenium, Astellas, Novartis, ProeteoMediX, Sanofi Aventis, and Pfizer and has a pending patent application for a method for biomarker WO 375 2009 138392 A1. Christian Rothermundt has received travel support from Janssen Cilag. Ralph Schiess has been CEO at ProteoMediX, owns ProteoMediX stock, and has a pending patent application for a method for biomarker WO 2009 138392 A1.

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