European Journal of Cancer 170 (2022) 285–295

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Statin and metformin use and outcomes in patients with castration-resistant prostate cancer treated with enzalutamide: A meta-analysis of AFFIRM, PREVAIL and PROSPER

Anthony M. Joshua [a,*,1], Andrew Armstrong [b,1], Megan Crumbaker [a], Howard I. Scher [c], Johann de Bono [d], Bertrand Tombal [e], Maha Hussain [f], Cora N. Sternberg [g], Silke Gillessen [h], Joan Carles [i], Karim Fizazi [j], Ping Lin [k], William Duggan [l], Jennifer Sugg [m], David Russell [n], Tomasz M. Beer [o]

[a] *Kinghorn Cancer Centre, St. Vincent's Hospital, Sydney, NSW, Australia*
[b] *Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC, USA*
[c] *Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[d] *The Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, London, UK*
[e] *Cliniques Universitaires Saint-Luc, Brussels, Belgium*
[f] *Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, USA*
[g] *Englander Institute for Precision Medicine, Weill Cornell Medicine, Meyer Cancer Center, New York, NY, USA*
[h] *Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland*
[i] *Vall D'Hebron University Hospital, Vall D'Hebron Institute of Oncology (VHIO), Barcelona, Spain*
[j] *Institut Gustave Roussy, University of Paris Saclay, Villejuif, France*
[k] *Formerly of Pfizer Inc., San Francisco, CA, USA*
[l] *Pfizer Inc., Groton, CT, USA*
[m] *Astellas Pharma, Inc., Northbrook, IL, USA*
[n] *Pfizer Inc., New York, NY, USA*
[o] *OHSU Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA*

Received 5 April 2021; received in revised form 30 March 2022; accepted 1 April 2022
Available online 26 May 2022

* *Corresponding author*: Kinghorn Cancer Centre, St Vincent's Hospital, 370 Victoria St, Darlinghurst, NSW 2010, Australia. Fax: +61293555602.
E-mail address: anthony.joshua@svha.org.au (A.M. Joshua).
[1] Dr Joshua and Armstrong contributed equally.

https://doi.org/10.1016/j.ejca.2022.04.005

KEYWORDS
Enzalutamide;
Castration-resistant prostate cancer;
Statin;
Metformin;
Radiographic progression-free survival;
Overall survival

Abstract ***Background:*** Statins and metformin are commonly prescribed for patients, including those with prostate cancer. Preclinical and epidemiologic studies of each agent have suggested anti-cancer properties.
Methods: Patient data from three randomised, double-blind, placebo-controlled, phase III studies evaluating enzalutamide (AFFIRM, PREVAIL and PROSPER) in patients with castration-resistant prostate cancer were included in this analysis. This *post hoc*, retrospective study examined the association of statin and metformin on radiographic progression-free survival (rPFS), metastasis-free survival (MFS), toxicity and overall survival (OS). After adjusting for available clinical prognostic variables, multivariate analyses were performed on pooled data from AFFIRM and PREVAIL, all three trials pooled, and each trial individually, to assess differential efficacy in these end-points associated with the baseline use of these medications.
Results: In the multivariate analysis of the individual trials, OS and rPFS/MFS were not significantly influenced by statin or metformin use in AFFIRM or PROSPER. However, in PREVAIL, OS was significantly influenced by statin (hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.59–0.89) and rPFS was significantly influenced by metformin (HR, 0.48; 95% CI 0.34–0.70). In pooled analyses, improved OS was significantly associated with statin use but not metformin use for AFFIRM+PREVAIL trials (HR 0.83; 95% CI 0.72–0.96) and AFFIRM+PREVAIL+PROSPER (HR 0.75; 95% CI 0.66–0.85).
Conclusions: The association between statin or metformin use and rPFS, MFS and OS was inconsistent across three trials. Analyses of all three trials pooled and AFFIRM+PREVAIL pooled revealed that statin but not metformin use was significantly associated with a reduced risk of death in enzalutamide-treated patients. Additional prospective, controlled studies are warranted.
Clinical trial registration: AFFIRM (NCT00974311), PREVAIL (NCT01212991) and PROSPER (NCT02003924).

1. Introduction

Cholesterol-lowering statin drugs and the antidiabetic drug metformin are among the two most frequently used concomitant medications in patients with prostate cancer [1,2]. Preclinical studies have shown these drugs to possess antitumour properties [3–8]. For example, statins induce apoptosis and cause G1 cell cycle arrest of prostate cancer cells through the inactivation of Ras homolog family member A [3]. *In vivo*, simvastatin reduces prostate tumour growth and prostate-specific antigen (PSA) expression through suppression of Akt activity [4]. Metformin has been thought to have pleotropic antitumor effects, including inhibition of complex 1 of the respiratory chain leading the 5' adenosine monophosphate-activated protein kinase inhibition, repression of epithelial-to-mesenchymal transition in prostate cancer cells by inhibiting signal transducer and activator of transcription-3 activation and transforming growth factor beta-1 production and inhibition of angiogenesis by downregulating platelet-derived growth factor B expression [5,6,8]. In a mouse model of prostate cancer, metformin delays cancer progression by inhibiting the infiltration of tumour-associated macrophages after androgen deprivation therapy (ADT) [7].

At the same time, multiple recent reports call attention to the risk of cardiovascular morbidity in patients treated with a variety of hormonal agents for prostate cancer. Randomised studies have suggested an increased risk in the setting of first-line hormonal therapy [9], as well as in treatment with next-generation hormonal agents [10].

There are mixed results for outcomes associated with statin use in patients with prostate cancer in epidemiologic and clinical studies [11,12]. For example, an observational study of 87,000 patients with prostate cancer showed that use of statins was associated with improved cancer-specific survival and overall survival (OS) in patients with advanced prostate cancer receiving ADT monotherapy [13]. Statin use by patients with metastatic castration-resistant prostate cancer (mCRPC) treated with cabazitaxel or mitoxantrone in the phase III TROPIC trial was associated with a longer OS, although no significant differences in progression-free survival or response rates were observed [14].

The reported effect of metformin on prostate cancer outcomes is likewise inconsistent [15–18]. For example, in a single-institution retrospective observational study, metformin use was associated with improved cancer-specific survival in patients with diabetes and prostate cancer in localised, early-stage disease [19]. However, two recent trials have suggested limited impact in established mCRPC. In the SAKK 08/09 study using

metformin as monotherapy, only 2/44 patients had a PSA_{50} response. In the recently presented TAXOMET study, 99 patients with mCRPC who were non-diabetic were randomised between standard docetaxel and prednisone and the addition of metformin (850 mg twice daily); no statistical differences were detected in this small study with limited duration of metformin in any clinically meaningful end-point [20]. One-third of the patients remained progression free at 12 weeks post-treatment with metformin and the PSA doubling time was prolonged in half of the patients [21].

Enzalutamide is a potent inhibitor of the androgen receptor, which blocks androgen binding, nuclear transport and DNA binding of the androgen-receptor complex [22]. It is approved to treat patients with CRPC and metastatic hormone-sensitive prostate cancer (HSPC) [23–26]. This is the first analysis from three large placebo-controlled phase III trials reporting the effects of statin or metformin use on efficacy outcomes of enzalutamide treatment in patients with CRPC. In interpreting any observations, consideration should be given to the possibility that statin or metformin may have an anti-cancer effect but, equally likely, they may modulate the risk of cardiovascular morbidity and mortality, a common occurrence in patients with prostate cancer.

2. Methods

2.1. Patients and study design

Patients from three previously published randomised, double-blind, placebo-controlled, phase III studies were included in the analysis; the study designs have been previously described [23,25–28]. AFFIRM (NCT00974311) enrolled patients with mCRPC previously treated with docetaxel who were randomised 2:1 to receive enzalutamide 160 mg per day or placebo. The primary end-point was OS. Radiographic progression-free survival (rPFS), defined as time from randomisation to radiographic progression, assessed by conventional imaging or death due to any cause specified by Prostate Cancer Clinical Trials Working Group 2 criteria, was a secondary end-point [26,29].

PREVAIL (NCT01212991) enrolled patients who were chemotherapy-naïve with mCRPC who were on continuing ADT and were randomised 1:1 to receive enzalutamide 160 mg or placebo once daily [25]. The coprimary end-points were rPFS, defined as time from randomisation to radiographic progression or death due to any cause within 168 days after treatment discontinuation, whichever occurred first, and OS.

PROSPER (NCT02003924) enrolled patients with non-metastatic CRPC with a PSA doubling time of $\leq$10 months who were on continuing ADT and were randomised 2:1 to receive 160 mg of enzalutamide or placebo once daily [23]. The primary end-point was metastasis-free survival (MFS), defined as the time from randomisation to radiographic progression, assessed by conventional imaging, or death due to any cause within 112 days after treatment discontinuation, whichever occurred first. OS was a secondary end-point. All studies were conducted in accordance with the Declaration of Helsinki and were approved by the ethics committee at each participating center. All patients provided written informed consent before enrolment.

2.2. Data sets

All analyses were carried out retrospectively on randomised patients with non-missing covariates who received the study drug. All analyses from AFFIRM were performed on data from the cut-off date of 25th September 2011 [26]. In PREVAIL, the rPFS analysis was performed on data from the cut-off date of 6th May 2012, and the OS from the data cut-off date of 16th September 2013 [25]. MFS and OS analyses from PROSPER were performed on data from the cut-off dates of 28th June 2017 and 20th December 2019, respectively [23,28]. Patients categorised into statin or metformin use were defined as those patients who were receiving a statin or metformin at baseline or post-baseline. Statin and metformin use was derived from a review of the baseline medications table in clinical study reports. Appropriate terms such as 'lipid modifying agents', 'amlodipine w/ atorvastatin', 'atorvastatin', 'fluvastatin', 'lovastatin', 'pitavastatin', 'pravastatin', 'rosuvastatin' and 'simvastatin' were used for statins and 'metformin' and 'metformin w/sitagliptin' were used for metformin.

2.3. Statistical analysis

Selected covariates were evaluated by univariate analysis to identify prognostic covariates significantly associated with efficacy outcomes. Multivariate Cox models were applied to the end-points using the covariates of interest, based on the work of Halabi *et al.* [30–32], as well as covariates identified through univariate analysis. Categorical covariates examined in the trials were treatment, Eastern Cooperative Oncology Group performance status (ECOG PS; 0 versus 1), disease site, lactate dehydrogenase, type 2 diabetes and diabetes other (includes type 2 diabetes mellitus, diabetes mellitus, hyperglycemia, glucose intolerance and insulin resistance), high cholesterol (defined as hypercholesterolaemia, hyperlipidaemia or dyslipidemia), prior cardiovascular disease (CVD; not for AFFIRM) and statin and metformin use. Continuous covariates included albumin, haemoglobin, log-transformed PSA, log-transformed alkaline

phosphatase, weight (for AFFIRM) and body mass index (BMI; for PREVAIL and PROSPER). The overall number of patients, the number (%) with events and the hazard ratios (HRs) for each covariate, along with their 95% confidence intervals (CIs), were derived. Cardiac adverse events (AEs) were defined according to the System Organ Class of Cardiac Disorders, and the number of events per patient-year was determined.

3. Results

3.1. Patients and characteristics

We retrospectively analysed 4277 patients across the three trials: AFFIRM (N = 1184), PREVAIL (N = 1699) and PROSPER (N = 1394) of whom 1321 patients (31%) had concomitant statin use (n = 209 [18%] from AFFIRM, n = 608 [36%] from PREVAIL and n = 504 [36%] from PROSPER) and 421 patients (10%) had used metformin (n = 52 [4%] from AFFIRM, n = 182 [11%] from PREVAIL and n = 187 [13%] from PROSPER). A total of 240 patients (5.6%) had both statin and metformin use (n = 23 [1.9%] from AFFIRM, n = 101 [5.9%] from PREVAIL, n = 116 [8.3%] in PROSPER). For each trial, demographics and disease characteristics were generally similar between patients receiving and those not receiving statins or metformin. With the exception of original indications for each drug (high cholesterol, type 2 diabetes and diabetes other, respectively), patients with metformin or statin use tended to be heavier with increased prevalence of CVD than those without metformin or statin use (Table 1).

3.2. Univariate analysis of selected covariates

Univariate analysis of OS and rPFS/MFS for the individual trials identified prior CVD, high cholesterol, BMI (PREVAIL and PROSPER) and weight (AFFIRM) as additional covariates for inclusion in the multivariate analysis (Supplementary Table 1). Weight (AFFIRM) and BMI (PREVAIL) showed significant association with OS (HR, 0.99; 95% CI 0.98–0.99; and HR, 0.96; 95% CI 0.94–0.98, respectively; $P < 0.0001$ for both) and BMI was significantly associated with rPFS/MFS in PREVAIL (HR, 0.98; 95% CI 0.96–1.00; $P = 0.03$). CVD showed a significant association with OS in PREVAIL (HR, 1.33; 95% CI 1.10–1.62; $P = 0.004$) and PROSPER (HR, 1.42; 95% CI 1.00–2.00; $P = 0.05$), and cholesterol was significantly associated with MFS in PROSPER only (HR, 0.81; 95% CI 0.66–1.00; $P = 0.04$). Even though diabetes was significantly associated with OS in AFFIRM (HR, 0.75; 95% CI 0.58–0.97; $P = 0.03$) and rPFS in AFFIRM (HR, 0.74; 95% CI 0.60–0.92; $P = 0.005$) and PREVAIL (HR, 0.76; 95% CI 0.59–0.99; $P = 0.04$), it was not included in the multivariate analysis due to significant overlap with metformin use (Table 1).

Multivariate analyses were performed on pooled data from AFFIRM+PREVAIL, all three trials pooled, and all three trials separately, with both drugs and prognostic factors as covariates to test whether the use of each agent was independently associated with differential efficacy. Herein, we report the associations.

3.3. Pooled multivariate analysis of OS

In the multivariate analysis of pooled data from AFFIRM+PREVAIL+PROSPER, statin but not metformin was significantly associated with a decreased risk of death or superior survival (OS HR, 0.75; 95% CI 0.66–0.85 and OS HR, 0.83; 95% CI 0.67–1.03, respectively) (Fig. 1a and Table 2), while enzalutamide use, ECOG PS, lactate dehydrogenase, albumin, haemoglobin, PSA and alkaline phosphatase were each independently associated with differential OS (Fig. 1a). The analysis of data by disease site demonstrated that patients with lymph node-only disease had significantly improved OS (HR, 0.46; 95% CI 0.38–0.57), whereas patients with visceral disease had significantly decreased OS (HR, 1.57; 95% CI 1.36–1.81). Weight did not significantly influence OS for the three trials pooled.

Similarly, multivariate analysis of pooled data from AFFIRM+PREVAIL showed that statin but not metformin use was significantly associated with improved OS with enzalutamide treatment (HR, 0.83; 95% CI 0.72–0.96 and HR, 0.79; 95% CI 0.62–1.02, respectively; Fig. 1b), while enzalutamide use, ECOG PS, lactate dehydrogenase, albumin, haemoglobin, PSA and alkaline phosphatase, were each independently associated with OS. Patients with visceral metastases were at higher risk of death compared with lymph node-only metastases (HR, 1.73; 95% CI 1.31–2.30). Weight did not significantly influence OS for the AFFIRM+PREVAIL trials pooled.

3.4. OS for AFFIRM, PREVAIL and PROSPER trials

Multivariate and univariate analyses of the individual trials demonstrated no disease-modifying effect of statin or metformin on OS in patients with CRPC treated with enzalutamide or placebo (Kaplan–Meier analyses of OS by statin and metformin use, Supplementary Fig. 2; univariate analyses of OS by statin and metformin use, Supplementary Figs. 3 and 4; univariate analysis of OS using the 2019 PROSPER cut-off, Supplementary Fig. 5); OS was not significantly influenced by statin or metformin use in AFFIRM (Fig. 1c and Table 2) or PROSPER (Fig. 1E and Table 2); more recent analysis of PROSPER data (cut-off December 20, 2019) yielded similar results (Supplementary Fig. 1). However, in PREVAIL, OS was significantly influenced by statin but not metformin (HR 0.72; 95% CI 0.59–0.89 and

Table 1
Patient demographics and disease characteristics by statin or metformin use at baseline.

	AFFIRM (N = 1184)				PREVAIL (N = 1699)				PROSPER (N = 1394)			
	Statin use		Metformin use		Statin use		Metformin use		Statin use		Metformin use	
	Yes (n = 209)	No (n = 975)	Yes (n = 52)	No (n = 1132)	Yes (n = 608)	No (n = 1091)	Yes (n = 182)	No (n = 1517)	Yes (n = 504)	No (n = 890)	Yes (n = 187)	No (n = 1207)
Treatment arm, n (%)												
Enzalutamide	139 (67)	650 (67)	34 (65)	755 (67)	315 (52)	548 (50)	90 (49)	773 (51)	344 (68)	585 (66)	126 (67)	803 (67)
Placebo	70 (34)	325 (33)	18 (35)	377 (33)	293 (48)	543 (50)	92 (51)	744 (49)	160 (32)	305 (34)	61 (33)	404 (33)
Median weight, kg	85.0	82.5	90.5	82.9	84.0	82.1	88.6	82.4	85.0	81.0	88.1	81.7
Median BMI, kg/m^2	NR	NR	NR	NR	28.1	27.1	29.6	27.2	28.6	27.1	29.3	27.4
Median systolic/diastolic blood pressure, mmHg	130/73	131/76	140/73	130/76	136/77	138/80	138/75	137/80	136/77	135/80	136/77	135/80
ECOG PS, n (%)												
0	80 (38)	368 (38)	17 (33)	431 (38)	388 (64)	773 (71)	117 (64)	1044 (69)	393 (78)	732 (82)	152 (81)	973 (81)
1	116 (56)	519 (53)	32 (62)	603 (53)	220 (36)	318 (29)	65 (36)	473 (31)	111 (22)	158 (18)	35 (19)	234 (19)
Prior CVD, n (%)	NR	NR	NR	NR	249 (41)	96 (9)	55 (30)	290 (19)	181 (36)	104 (12)	52 (28)	233 (19)
High cholesterol[a] n (%)	115 (55)	129 (13)	15 (29)	229 (20)	319 (52)	73 (7)	55 (30)	337 (22)	193 (38)	51 (6)	46 (25)	198 (16)
Type 2 diabetes, n (%)	36 (26)	69 (11)	34 (100)	71 (9)	76 (24)	51 (9)	82 (91)	45 (6)	105 (31)	71 (12)	113 (90)	63 (8)
Diabetes other (%)[b]	37 (27)	80 (12)	34 (100)	83 (11)	87 (28)	61 (11)	84 (93)	64 (8)	110 (32)	78 (13)	116 (92)	72 (9)
Baseline use of opioids, n (%)	0	0	0	0	0	0	0	0	32 (6)	33 (4)	15 (8)	50 (4)
Disease location, n (%)												
LN only	14 (7)	51 (5)	0	65 (6)	86 (14)	145 (13)	28 (15)	203 (13)	NA	NA	NA	NA
Bone ± LN	139 (67)	703 (72)	36 (69)	806 (71)	447 (74)	817 (75)	130 (71)	1134 (75)	NA	NA	NA	NA
Any visceral	56 (27)	221 (23)	16 (31)	261 (23)	75 (12)	129 (12)	24 (13)	180 (12)	NA	NA	NA	NA
High LDH, n (%)	80 (38)	381 (39)	16 (31)	445 (39)	100 (16)	187 (17)	22 (12)	265 (17)	40 (8)	59 (7)	5 (3)	94 (8)
Median PSA, ng/mL	99.3	118.0	92.4	113.8	51.9	49.6	46.4	51.0	10.9	10.5	9.3	10.8
Median testosterone, nmol/L	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	NR	NR	NR	NR
Median neutrophils, GI/L	4.3	4.2	4.3	4.2	4.1	4.0	4.3	4.0	3.9	3.7	4.1	3.7
Median lymphocytes, GI/L	1.2	1.2	1.2	1.2	1.6	1.6	1.6	1.5	1.6	1.6	1.7	1.6

BMI, body mass index; CVD, cardiovascular disease; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; LN, lymph node; NR, not reported; NA, not applicable; PSA, prostate-specific antigen.

[a] High cholesterol defined as patients with hypercholesterolaemia, hyperlipidaemia, or dyslipidemia.

[b] Diabetes other includes type 2 diabetes mellitus, diabetes mellitus, hyperglycemia, glucose intolerance, and insulin resistance.

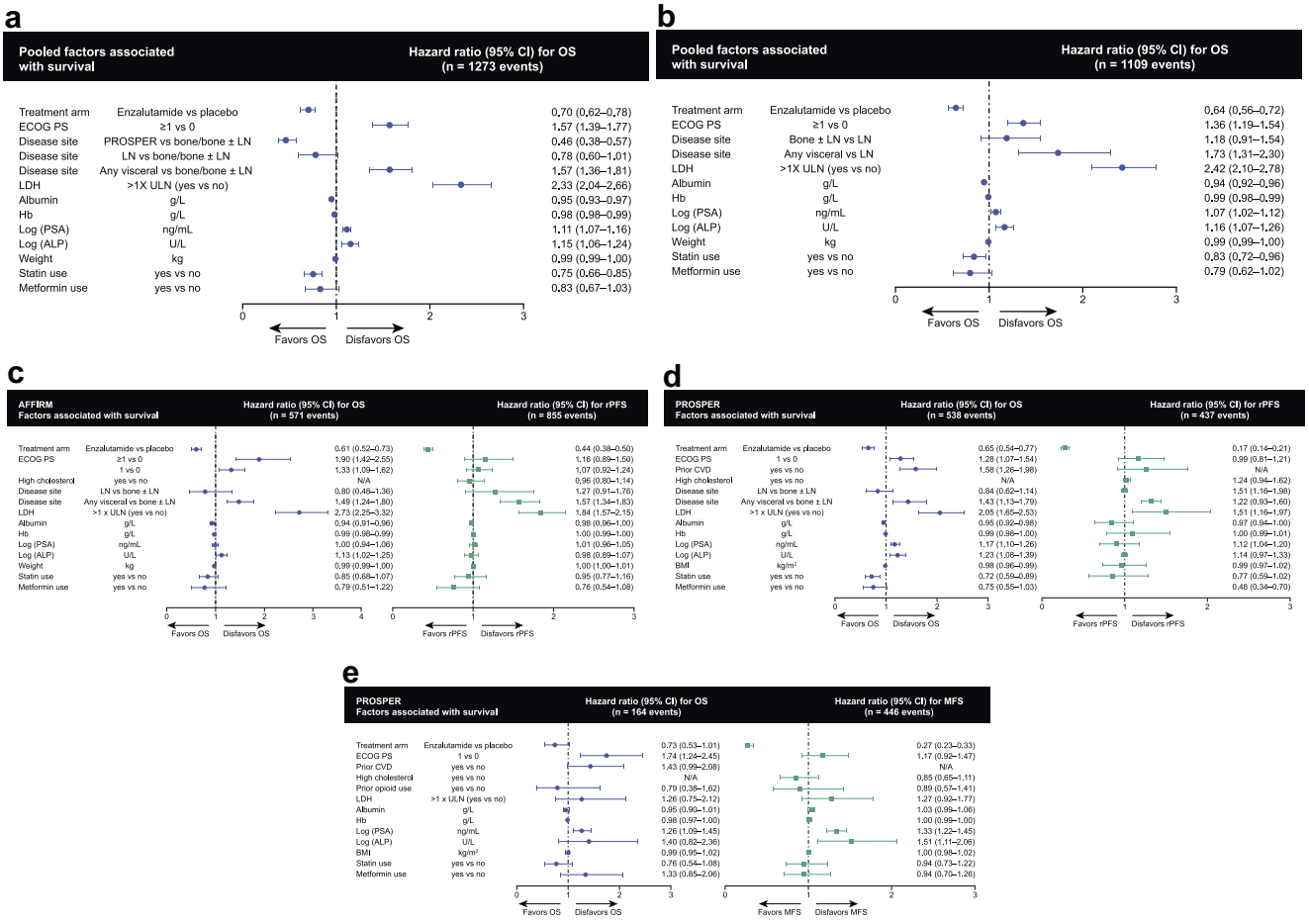


Fig. 1. Multivariate analysis of (**a**) AFFIRM+PREVAIL+PROSPER pooled (**b**) AFFIRM+PREVAIL pooled, (**c**) AFFIRM, (**d**) PREVAIL, and (**e**) PROSPER. ALP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; ECOG PS, Eastern Cooperative Oncology Group performance status; Hb, haemoglobin; LDH, lactate dehydrogenase; LN, lymph node; MFS, metastasis-free survival; OS, overall survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; ULN, upper limit of normal.

HR 0.75; 95% CI 0.55–1.03, respectively, Fig. 1d and Table 2).

ECOG PS was associated with reduced OS for all three individual trials (Fig. 1c–e). Prior CVD was significantly associated with reduced OS in PREVAIL (HR, 1.58; 95% CI 1.26–1.98) but not in PROSPER. Patients with visceral metastases were at higher risk of death compared with lymph node-only metastases in AFFIRM (HR, 1.49; 95% CI 1.24–1.80; Fig. 1c) and PREVAIL (HR, 1.43; 95% CI 1.13–1.79; Fig. 1d). Disease site data were not available for the PROSPER trial as the study population consisted of patients with non-metastatic disease. Other factors associated with slight improvements in OS were albumin (AFFIRM and PREVAIL) and haemoglobin (AFFIRM), reduced OS was associated with lactate dehydrogenase (for AFFIRM and PREVAIL), PSA (for PREVAIL and PROSPER) and alkaline phosphatase (for AFFIRM and PREVAIL). Weight did not significantly influence OS in AFFIRM, nor did BMI influence OS in PROSPER (Fig. 1c and e). However, BMI had a slight but significant influence on OS in PREVAIL (HR, 0.98; 95% CI 0.96–0.99; Fig. 1d).

3.5. rPFS and MFS for AFFIRM, PREVAIL and PROSPER trials

Multivariate and univariate analyses of the individual trials did not provide consistent evidence of a disease-modifying effect for statin or metformin on radiographic time to event end-points in patients with CRPC treated with enzalutamide or placebo (Kaplan–Meier analyses of rPFS/MFS and by statin and metformin use are presented in Supplementary Fig. 6; for univariate analyses of rPFS/MFS and OS by statin and metformin use, see Supplementary Figs. 3 and 4). rPFS was not significantly influenced by statin or metformin use in AFFIRM (Fig. 1c and Table 2), nor was MFS significantly influenced by statin or metformin use in PROSPER (Fig. 1e and Table 2). In the PREVAIL trial (Fig. 1d and Table 2), rPFS was not significantly influenced by statin use, however, metformin use significantly improved rPFS

Table 2
Multivariate analysis on the association of statin or metformin with rPFS or MFS and OS in patients with CRPC receiving enzalutamide or placebo.

	AFFIRM (N = 1184)				PREVAIL (N = 1699)				PROSPER (N = 1394)				POOLED ANALYSIS OF ALL 3 TRIALS (N = 4277)			
	Statin use		Metformin use		Statin use		Metformin use		Statin use		Metformin use		Statin use		Metformin use	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
rPFS or MFS	0.95	0.77–1.16	0.76	0.54–1.08	0.77	0.59–1.02	0.48	0.34–0.70	0.94	0.73–1.22	0.94	0.70–1.26	N/A	N/A	N/A	N/A
OS	0.85	0.68–1.07	0.79	0.51–1.22	0.72	0.59–0.89	0.75	0.55–1.03	0.76	0.54–1.08	1.33	0.85–2.06	0.75	0.66–0.85	0.83	0.67–1.03

CI, confidence interval; CRPC, castration-resistant prostate cancer; HR, hazard ratio; NA, not available; MFS, metastasis-free survival; OS, overall survival; rPFS, radiographic progression-free survival.

with enzalutamide treatment (HR, 0.48; 95% CI, 0.34–0.70; Fig. 1d and Table 2).

Factors that decreased rPFS for AFFIRM included lactate dehydrogenase and presence of visceral metastases (Fig. 1c). For PREVAIL (Fig. 1d), lactate dehydrogenase, PSA and lymph node metastases decreased rPFS. Alkaline phosphatase and PSA were factors that decreased MFS for PROSPER (Fig. 1e). High cholesterol, weight (in AFFIRM) and BMI (in PREVAIL and PROSPER) did not have a significant influence on rPFS/MFS.

3.6. Safety

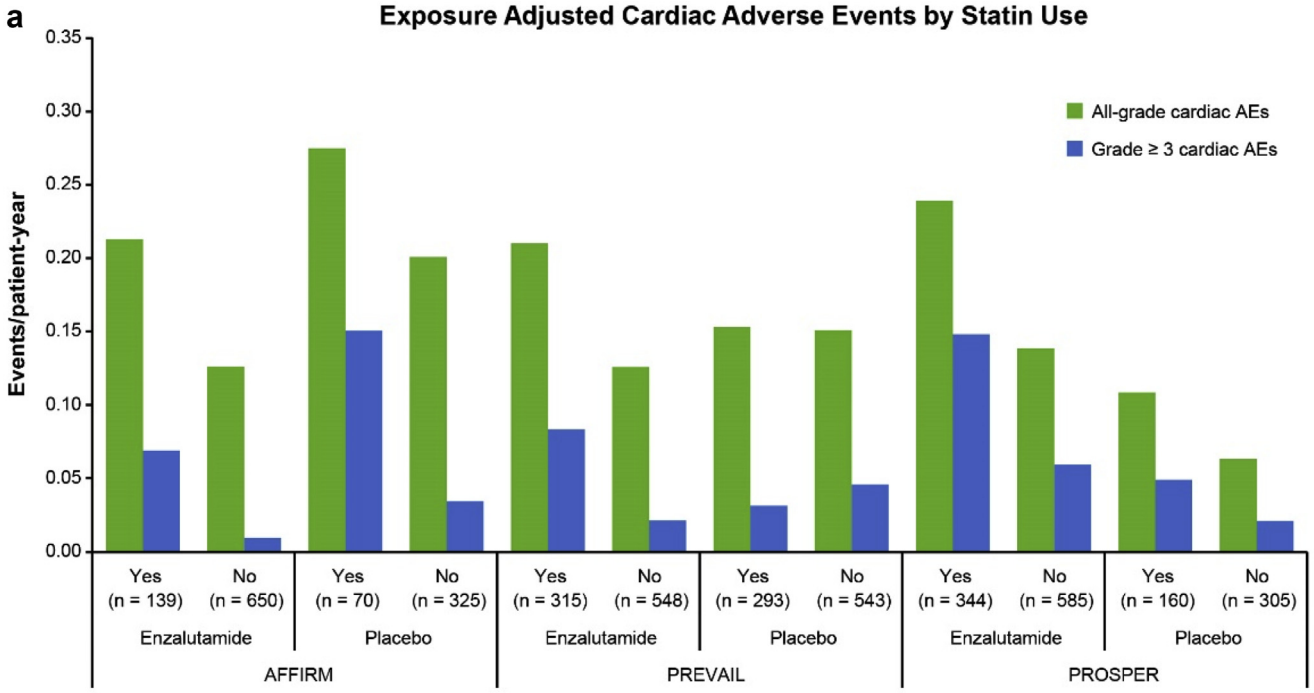
Across the three trials, patients with statin use reported a higher incidence of cardiac AEs compared with those without statin use (any grade exposure-adjusted rates ranged from 0.06 to 0.28 per patient-year; Grade ≥3 exposure-adjusted rates ranged from 0.01 to 0.15 per patient-year), except in the placebo arm of PREVAIL, where the rates were similar (any grade rates of 0.15 per patient-year in both cohorts; Grade ≥3 rates 0.03 versus 0.05 per patient-year, respectively, Fig. 2a). At the 2019 PROSPER data cut-off, exposure adjusted rates were 0.03–0.09 and 0.01–0.06 for any grade and Grade ≥3 cardiac AEs, respectively (Supplementary Fig. 7A).

The relationship between exposure-adjusted cardiac AEs and metformin use was less consistent (any grade rates ranged from 0.06 to 0.30; Grade ≥3 rates ranged from 0.02 to 0.17). Patients in the enzalutamide arms using metformin generally had higher cardiac AE rates than those not using metformin. However, in the placebo arms of AFFIRM and PROSPER, patients using metformin had lower cardiac AE rates versus those not using metformin after adjusting for exposure. It should be noted, however, that the number of patients with metformin use was low (Fig. 2b and Supplementary Fig. 7B). These patterns were generally replicated both for all cardiac events and those Grade ≥3.

Most patients died from progressive disease, regardless of statin or metformin use (Supplementary Tables 2 and 3). There were no obvious trends in the causes of death in any of the trials based on statin or metformin use.

4. Discussion

Despite multiple preclinical and epidemiological studies [3–8], clinical evidence of benefit of the use of metformin and statins in patients with advanced or metastatic prostate cancer is lacking. Here, we analysed three global, randomised, phase III trials to examine whether statin or metformin use was associated with improved radiographic endpoints or OS in patients with CRPC, ranging from mCRPC post-docetaxel (AFFIRM, NCT00974311), pre-docetaxel



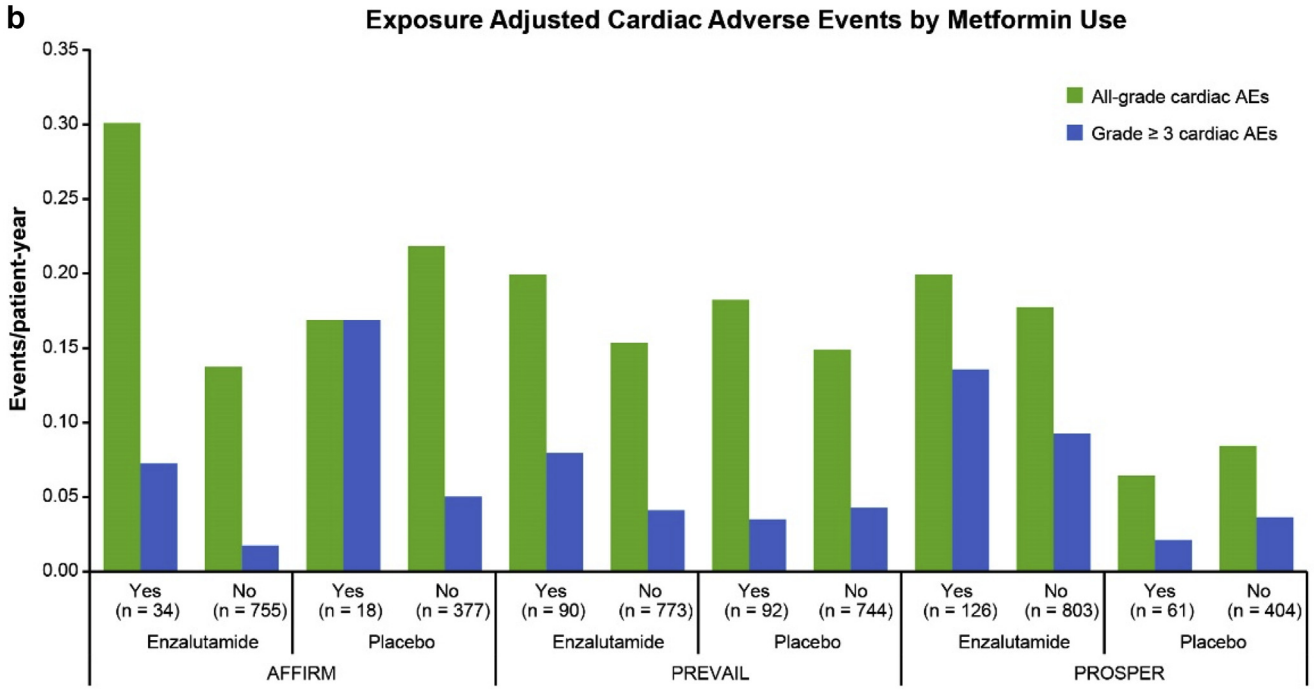


Fig. 2. Exposure-adjusted cardiac AEs[a] by (**a**) statin or (**b**) metformin use.[a]As defined by the System Organ Class of Cardiac Disorders. Data cut-off date for PROSPER was September, 2017. AE, adverse event.

(PREVAIL, NCT01212991) and finally high-risk non-metastatic CRPC (PROSPER, NCT02003924), all of which achieved superiority over their respective control arms [23,25–28,33].

Even with access to data from three of the largest clinical trials in advanced prostate cancer, our ability to detect a modest effect is limited and is complicated by the non-random nature of the decision to prescribe statins or metformin. Health imbalances, particularly cardiovascular and metabolic conditions, between statin and metformin users could not be fully accounted for. Additional limitations to this analysis include lack of data about continuation of treatment, including ADTs, or new prescriptions after enrolment and inability to

assess the exposure duration. Thus, although the pooled multivariate analysis suggests that statins are associated with improved OS after adjustment for enzalutamide treatment and common prognostic factors, this finding is subject to significant limitations. There are prospective clinical trials of each agent currently underway (PEACE-4 for atorvastatin and aspirin [NCT03819101] in patients with mCRPC, STAMPEDE for metformin [NCT00268476] in patients with mCRPC and MAST for metformin in patients receiving active surveillance [NCT01864096]), and it remains plausible that the benefits of the drugs in unselected populations will be too minor to reach a level of clinical utility.

Our data on cardiac toxicity associated with the co-administration of either drug are likely heavily confounded by the baseline cardiovascular risk and original indication for either drug, but they do highlight the impact of cardiovascular mortality in this population, an increasingly recognised challenge in prostate cancer hormonal therapy.

To date, other trials examining the concomitant use of novel androgen signalling inhibitors and the effect of concomitant medications have been limited. In the COU301 and COU302 studies with patients in the mCRPC setting, statin use was associated with improved OS study [34,35]. We also note the recent presentation of the MANSMED study, a randomised, single-blinded trial of metformin plus standard combined hormone treatment in patients with HSPC. This study demonstrated that patients receiving metformin had a longer time to castration-resistant disease (median 29 months, 95% CI 25–33) compared with those randomised to placebo (20 months, 95% CI 16–24, $P = 0.01$). This effect seemed to be most pronounced in patients with high-risk localised disease and node-positive disease and marginal in those with low-volume metastatic disease, and there seemed to be no benefit in those with high-volume metastatic disease [36]. Thus, if this and the STAMPEDE results confirm a benefit to metformin, these data suggest that efficacy results may differ for concurrent metformin use in the HSPC versus the CRPC settings.

While it is possible that drugs such as statins or metformin have their greatest effect in early mCRPC, or possibly in hormone-sensitive disease, the inconsistency of effect in earlier stages of disease (PROSPER) or within the control arm suggest this effect, if any, is not robust or deep enough in the population already receiving these drugs for pre-existent conditions to be clinically indicated. Further insights, such as biomarkers of efficacy, would be required to ascertain their role within prostate cancer outside their traditional utility in cardiovascular risk reduction and glucose intolerance, respectively.

Author contributions

AMJ, AA, HIS, PL, TMB: concept and design, collection and assembly of data, data analysis and interpretation; JDB, BT: concept and design, data analysis and interpretation; MH, DR: collection and assembly of data, data analysis and interpretation; CNS, SG, JC, KF, WD, JS: data analysis and interpretation; MC: data review and interpretation. All authors contributed to manuscript preparation, editing and review, and are accountable for all aspects of the work.

Data sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Conflict of interest statement

AMJ declares consultant/advisory board member for Neokulin, Janssen Oncology, Ipsen, AstraZeneca, Sanfoi, Noxopharm, IQvia, Pfizer, Novartis, Bristol Myers Squibb, Merck Serono, Eisai. AMJ has received research funding from: Bristol Myers Squibb, Janssen Oncology, Merck Sharp & Dohme, Mayne Pharma, Roche/Genetech, Bayer, Macrogenics, Lilly, Pfizer, AstraZeneca, and Corvus Pharmaceuticals.

AA is a paid consultant for and/or receives institutional funding from Astellas, Pfizer, Janssen, Bayer, Dendreon, Genentech/Roche, Bristol Myers Squibb, Merck, and AstraZeneca. AA provides research support to Duke University from Constellation, Beigene, Amgen, Celgene, and Forma.

MC has received honoraria from Pfizer and Merck Healthcare.

HIS declares consultant/advisory board member for Ambry Genetics Corporation, Amgen, Bayer, ESSA Pharma, Janssen Biotech, Janssen Research & Development, OncLive Insights, Menarini Silicon Biosystems, Physicians Education Resource, Pfizer, Sanofi Aventis, Sun Pharmaceuticals Industries, Inc. and WCG Oncology; Board of Directors' Member of Asterias Biotherapeutics; Intellectual Property Rights BioNTech, Elucida Oncology, MaBVAX, Y-mAbs Therapeutics, Inc and institutional research funding from Epic Sciences, Illumina, Janssen Diagnostics, Menarini Silicon Biosystems, and ThermoFisher.

JDB has served on advisory boards and received fees from Amgen, Astellas, AstraZeneca, Bayer, Bioxcel

Therapeutics, Boehringer Ingelheim, Cellcentric, Daiichi, Eisai, Genentech Roche, Genmab, GlaxoSmithKline, Harpoon, Janssen, Menarini Silicon Biosystems, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer, Qiagen, Sanofi Aventis, Sierra Oncology, Taiho, Terumo, Vertex Pharmaceuticals. He is an employee of the ICR, which has received funding or other support for his research work from Astellas, AstraZeneca, Bayer, Cellcentric, Daiichi, Genentech Roche, Genmab, GlaxoSmithKline, Harpoon, Janssen, Merck Serono, Merck Sharp & Dohme, Orion Pharma, Pfizer, Sanofi Aventis, Sierra Oncology, Taiho, Vertex Pharmaceuticals, and which has a commercial interest in abiraterone, PARP inhibition in DNA repair defective cancers and PI3K/AKT pathway inhibitors (no personal income). He was named as an inventor, with no financial interest, for patent 8,822,438.

BT has financial or personal interests with AAA International, Astellas, Bayer, Ferring, Janssen, Myovant and Sanofi.

MH over the last three years reports receiving lecture fees and travel support from Astellas Pharma, grant support, paid to Northwestern University, from AstraZeneca, grant support, paid to Northwestern University, and advisory board fees from Bayer, advisory board fees from Daiichi Sankyo, Bristol Myers Squibb, grant support, paid to Northwestern University, and advisory board fees from Genentech, grant support, paid to the University of Michigan, from Pfizer, and lecture fees from Sanofi and Genzyme.

CNS is a consultant for Pfizer, Merck Sharp & Dohme, Merck, AstraZeneca, Astellas, Sanofi-Genzyme Roche-Genentech, Incyte, Clovis Oncology, Inc, Medscape, UroToday, Janssen Oncology, Foundation Medicine, Bristol Meyers Squibb, Immunomedics (now Gilead).

SG in the last three years has received honoraria compensation from Janssen Cilag; served in a consulting or advisory role (including IDMC) to Astellas Pharma, Amgen, Roche, Pfizer, AAA International, Janssen, Innocrin Pharma Inst, Sanofi, Bayer, Orion Pharma GmbH, Clovis Oncology, Menarini Silicon Biosystems, Tolero Pharmaceuticals and Merck Sharp & Dohme; Patents, royalties, other intellectual property include Method for biomarker WO2009138392; Travel grant from ProteoMediX; Other relationships include Aranda.

JC is a paid consultant with Amgen, Astellas, Bayer, Bristol Myers Squibb, Merck Sharp & Dohme, Johnson & Johnson, Sanofi, Pfizer; is a member of the Speakers Bureau for Astellas, Bayer, Johnson & Johnson; has engaged in institutional study collaboration with AB Science, Aragon Pharmaceuticals, Arog Pharmaceuticals, Inc, Astellas Pharma., AstraZeneca AB, Aveo Pharmaceuticals Inc, Bayer AG, Blueprint Medicines Corporation, BN Immunotherapeutics Inc, Boehringer Ingelheim España, S.A., Bristol Myers Squibb International Corporation, Clovis Oncology, Inc, Cougar Biotechnology Inc, Deciphera Pharmaceuticals LLC, Exelixis Inc, F. Hoffmann-La Roche LTD, Genentech Inc, Glaxosmithkline, SA, Incyte Corporation, Janssen-Cilag International NV, Karyopharm Therapeutics Inc, Laboratoires Leurquin Mediolanum SAS, Lilly, S.A., Medimmune, Millennium Pharmaceuticals, Inc, Nanobiotix SA, Novartis Farmacéutica, S.A., Pfizer, S.L.U, Puma Biotechnology, Inc, Sanofi-Aventis, S.A., SFJ Pharma LTD. II, Teva Pharma S.L.U.

KF has participated on advisory boards and symposia for: Astellas, Bayer, Clovis, Curevac, Janssen, Merck Sharp & Dohme, Orion, Sanofi.

PL declares no conflict of interest.

WD is an employee of Pfizer and owns stock in the company.

JS is an employee of Astellas.

DR is an employee of Pfizer.

TMB in the past year reports: institutional research funding from Alliance Foundation Trials, Astellas Pharma, Bayer, Boehringer Ingelheim, Corcept Therapeutics, Endocyte Inc., Freenome, Grail Inc, Harpoon Therapeutics, Janssen Research & Development, Medivation, Inc., Sotio, Theraclone Sciences/OncoResponse, and Zenith Epigenetics; has consulted for: Arvinas, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Constellation, Grail Inc, Janssen, Myovant Sciences, Pfizer, and Sanofi, and holds stock in Arvinas Inc, and Salarius Pharmaceuticals.

Acknowledgments

This study was sponsored by Pfizer Inc. (New York, NY, USA) and Astellas Pharma, Inc. (Northbrook, IL, USA), the co-developers of enzalutamide. Medical writing and editorial support funded by the sponsors were provided by Stephanie Vadasz, PhD, and Dena McWain of Ashfield MedComms (an Ashfield Health company), Lauren Rainer, BSc, and Julie B. Stimmel, PhD, of Onyx (a Prime Global agency).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.04.005.

References

[1] Winters B, Plymate S, Zeliadt SB, Holt S, Zhang X, Hu E, et al. Metformin effects on biochemical recurrence and metabolic signaling in the prostate. Prostate 2015;75:1694–703.

[2] Li H, Hodgson E, Watson L, Shukla A, Nelson JJ. Comorbidities and concomitant medication use in men with prostate cancer or high levels of PSA compared to matched controls: a GPRD analysis. J Cancer Epidemiol 2012:291704.

[3] Hoque A, Chen H, Xu XC. Statin induces apoptosis and cell growth arrest in prostate cancer cells. Cancer Epidemiol Biomarkers Prev 2008;17:88–94.

[4] Kochuparambil ST, Al-Husein B, Goc A, Soliman S, Somanath PR. Anticancer efficacy of simvastatin on prostate cancer cells and tumor xenografts is associated with inhibition of Akt and reduced prostate-specific antigen expression. J Pharmacol Exp Ther 2011;336:496–505.
[5] Wang JC, Li GY, Wang B, Han SX, Sun X, Jiang YN, et al. Metformin inhibits metastatic breast cancer progression and improves chemosensitivity by inducing vessel normalization via PDGF-B downregulation. J Exp Clin Cancer Res 2019;38:235.
[6] Wang Y, Liu G, Tong D, Parmar H, Hasenmayer D, Yuan W, et al. Metformin represses androgen-dependent and androgen-independent prostate cancers by targeting androgen receptor. Prostate 2015;75:1187–96.
[7] Liu Q, Tong D, Liu G, Gao J, Wang LA, Xu J, et al. Metformin inhibits prostate cancer progression by targeting tumor-associated inflammatory infiltration. Clin Cancer Res 2018;24:5622–34.
[8] Liu Q, Tong D, Liu G, Xu J, Do K, Geary K, et al. Metformin reverses prostate cancer resistance to enzalutamide by targeting TGF-beta1/STAT3 axis-regulated EMT. Cell Death Dis 2017;8:e3007.
[9] Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med 2020;382:2187–96.
[10] Iacovelli R, Ciccarese C, Bria E, Romano M, Fantinel E, Bimbatti D, et al. The cardiovascular toxicity of abiraterone and enzalutamide in prostate cancer. Clin Genitourin Cancer 2018;16:e645–53.
[11] Mikkelsen MK, Thomsen FB, Berg KD, Jarden M, Larsen SB, Hansen RB, et al. Associations between statin use and progression in men with prostate cancer treated with primary androgen deprivation therapy. Scand J Urol 2017;51:464–9.
[12] Larsen SB, Dehlendorff C, Skriver C, Dalton SO, Jespersen CG, Borre M, et al. Postdiagnosis statin use and mortality in Danish patients with prostate cancer. J Clin Oncol 2017;35:3290–7.
[13] Anderson-Carter I, Posielski N, Liou JI, Khemees TA, Downs TM, Abel EJ, et al. The impact of statins in combination with androgen deprivation therapy in patients with advanced prostate cancer: a large observational study. Urol Oncol 2019;37:130–7.
[14] Lorente D, De Velasco Oria GA, Carles J, Gillessen S, Fizazi K, Joshua A, et al. Statin use and outcome in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) treated in the TROPIC trial. Ann Oncol 2018;29:viii279–80.
[15] Bensimon L, Yin H, Suissa S, Pollak MN, Azoulay L. The use of metformin in patients with prostate cancer and the risk of death. Cancer Epidemiol Biomarkers Prev 2014;23:2111–8.
[16] Stopsack KH, Ziehr DR, Rider JR, Giovannucci EL. Metformin and prostate cancer mortality: a meta-analysis. Cancer Causes Control 2016;27:105–13.
[17] Hankinson SJ, Fam M, Patel NN. A review for clinicians: prostate cancer and the antineoplastic properties of metformin. Urol Oncol 2017;35:21–9.
[18] Whitburn J, Edwards CM, Sooriakumaran P. Metformin and prostate cancer: a new role for an old drug. Curr Urol Rep 2017;18:46.
[19] Spratt DE, Zhang C, Zumsteg ZS, Pei X, Zhang Z, Zelefsky MJ. Metformin and prostate cancer: reduced development of castration-resistant disease and prostate cancer mortality. Eur Urol 2013;63:709–16.
[20] Pujalte-Martin M, Borchiellini D, Viotti J, Guillot A, Baptiste-Paoli J, Besson D, et al. TAXOMET: a French prospective multicenter randomized controlled phase II study comparing docetaxel plus metformin versus docetaxel plus placebo in mCRPC. J Clin Oncol 2019;37:5004.
[21] Rothermundt C, Hayoz S, Templeton AJ, Winterhalder R, Strebel RT, Bartschi D, et al. Metformin in chemotherapy-naive castration-resistant prostate cancer: a multicenter phase 2 trial (SAKK 08/09). Eur Urol 2014;66:468–74.
[22] Schalken J, Fitzpatrick JM. Enzalutamide: targeting the androgen signalling pathway in metastatic castration-resistant prostate cancer. BJU Int 2016;117:215–25.
[23] Hussain M, Fizazi K, Saad F, Rathenborg P, Shore N, Ferreira U, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465–74.
[24] Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019;37:2974–86.
[25] Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33.
[26] Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[27] Armstrong AJ, Lin P, Tombal B, Saad F, Higano CS, Joshua AM, et al. Five-year survival prediction and safety outcomes with enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer from the PREVAIL trial. Eur Urol 2020;78:347–57.
[28] Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020;382:2197–206.
[29] Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1148–59.
[30] Halabi S, Vogelzang NJ, Ou SS, Owzar K, Archer L, Small EJ. Progression-free survival as a predictor of overall survival in men with castrate-resistant prostate cancer. J Clin Oncol 2009;27:2766–71.
[31] Halabi S, Lin CY, Small EJ, Armstrong AJ, Kaplan EB, Petrylak D, et al. Prognostic model predicting metastatic castration-resistant prostate cancer survival in men treated with second-line chemotherapy. J Natl Cancer Inst 2013;105:1729–37.
[32] Halabi S, Lin CY, Kelly WK, Fizazi KS, Moul JW, Kaplan EB, et al. Updated prognostic model for predicting overall survival in first-line chemotherapy for patients with metastatic castration-resistant prostate cancer. J Clin Oncol 2014;32:671–7.
[33] Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL study. Eur Urol 2017;71:151–4.
[34] Velasco Gd, Lora D, Lorente D, Choueiri TK, Sweeney C, Castellano DE. Impact of statins on outcomes in patients (pts) with metastatic castration resistant prostate cancer (mCRPC): post-hoc analysis of data from COU-AA-301 and COU-AA-302 trials. J Clin Oncol 2018;36(Suppl 6):230.
[35] Hamilton RJ, Li J, Naini V, Kheoh TS, Porre PD, Molina A, et al. Effect of concomitant medication use on outcomes of treatment and placebo arms of the COU-AA-301 and COU-AA-302 studies of abiraterone acetate (AA) in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2014;32:e16045.
[36] Alghandour R, Ebrahim MA, Elshal AM, Ghobrial F, Elzaafaranyu M, Elbaiomy M. MANSMED: repurposing metformin as an anticancer drug: preliminary results of randomized controlled trial in advanced prostate cancer. Ann Oncol 2020;31(Suppl 4):S511.