Uncontrolled diabetes predicts poor response to novel antiandrogens

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Abstract

Metabolic abnormalities including hyperglycemia and hyperlipidemia have been associated with worse prognosis of prostate cancer (PCa), but there are limited data regarding their impact on the prognosis of castrate-resistant prostate cancer (CRPC) and the response of novel antiandrogens, namely abiraterone acetate (AA) and enzalutamide. Retrospective analysis of 61 patients with CRPC on AA or enzalutamide, treated at the Boston Medical Center, was performed. We evaluated hemoglobin A1c (HbA1c), HDL, LDL, Triglycerides and BMI within 2 months before the initiation of treatment with AA or enzalutamide and progression-free survival (PFS) under this treatment. Regression analysis and analysis of variance were used to evaluate the data. HbA1c levels were found to predict adversely the PFS on the novel agents (df (1, 37), $P=0.00$, $R^2=0.40$, coeff $=-3.28$). The Kaplan–Meier analysis showed that there is significant difference in survival between the HbA1c 4.7–5.9% compared with patients with HbA1c 7.8–11.6% (6.72 ± 1.3 months, log rank test $P<0.0001$) LDL ($P=0.07$), HDL ($P=0.14$), and triglycerides ($P=0.33$) were not found to predict PFS. BMI predicted PFS positively (df (1.59), $P=0.02$, $R^2=0.09$, coeff $=0.03$), but not independently of HbA1c ($P=0.07$). No significant implications of social and family history, previous chemotherapy regimen, and Gleason score with PFS were found. Multiple markers of patients' health state were not associated with HbA1c values. Uncontrolled diabetes can predict for poor response of CRPC patients to AA and enzalutamide determining PFS under this treatment. Elevated BMI can positively affect PFS at this stage of disease.

Key Words
- castrate-resistant prostate cancer
- diabetes
- abiraterone acetate
- enzalutamide
- HbA1c

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Introduction

Castrate-resistant prostate cancer (CRPC), defined as prostate cancer (PCa) progressing under systemic androgen deprivation therapy (ADT), remains an incurable disease (Wu *et al.* 2014). Abiraterone acetate (AA) and enzalutamide are novel antiandrogens approved for chemotherapy-naïve patients with CRPC, but the survival benefit for them is <5 months (Ryan *et al.* 2013, Evans *et al.* 2016). Despite the extensive research efforts, there are currently no known predictive markers of response to AA and enzalutamide, which could be particularly useful for stratifying patients with CRPC and guiding appropriate treatment such as chemotherapy or further androgen receptor (AR) inhibition.

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Recent studies have identified an association between metabolic abnormalities such as hyperglycemia and hyperlipidemia with PCa development and aggressiveness (Magura *et al*. 2008, Wright *et al*. 2013). Insulin resistance and hyperinsulinemia are associated with more aggressive disease and increased incidence of recurrence (Hammarsten & Hogstedt 2004, Kheterpal *et al*. 2013). Consistent with these findings, time to CRPC is shorter in patients with metabolic syndrome compared with those without similar metabolic abnormalities (Flanagan *et al*. 2011). Obesity, hyperlipidemia, hyperinsulinemia and diabetes at the time of PCa diagnosis are associated with increased disease-associated mortality (Hammarsten & Hogstedt 2005, Ma *et al*. 2008). Thus, metabolic abnormalities related to insulin resistance at the time of diagnosis or in early disease stages, may be related to worse prognosis. However, there are scarce and ambiguous data regarding the implications of metabolic abnormalities in the prognosis and response to novel hormonal therapies for CRPC patients (Halabi *et al*. 2007, Conteduca *et al*. 2015). Those conclusions would be of particular importance since androgen deprivation therapy (ADT) has been shown to induce insulin resistance (Yu *et al*. 2014).

Taking the above in their totality, there is evidence that metabolic abnormalities are implicated in the PCa development and progression. Currently, it is imperative to identify objective biomarkers to predict the sensitivity to novel antiandrogens and guide clinicians in the decision-making process in CRPC patients. The aim of our study was to evaluate the effects of metabolic status on response to AA and enzalutamide and identify widely tested metabolic markers to predict the response to these novel hormonal therapies in CRPC patients.

Patients and methods

Patients

In this retrospective study with Institutional Review Board approval, we analyzed medical records of patients with CRPC who received AA or enzalutamide at the Boston University Medical Center. CRPC was defined as biochemical, clinical or radiological progression on ADT with castrate serum testosterone levels <50 ng/dL. Progression on novel antiandrogens was clinical, biochemical, or radiological. Progression-free survival (PFS) was used as a marker of response to treatment with novel antiandrogens and it is defined as the months on treatment since the agent was changed when the patients developed progression (Loriot *et al*. 2015).

Data collection

Data collection was between January 2010 and September 2015 (data of last follow-up). For each patient, data were collected from a retrospective review of his or her medical records. The following variables were recorded for analysis: age, race, smoking and alcohol history, family history of diabetes, and cardiovascular disease, performance status (based on the Eastern Cooperative Oncology Group (ECOG)) (Sorensen *et al*. 1993), level of pain (based on the FACES Pain Rating Scale) (Breivik *et al*. 2008), comorbidities (cardiovascular disease, cerebrovascular accidents, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary obstructive disease (COPD), chronic kidney disease, hemiplegia, leukemia, lymphoma, other cancer, liver disease, acquired immunodeficiency syndrome), Charlson Comorbidity Index (CCI) (Charlson *et al*. 1987), Gleason score, presence of metastases (lymph nodes, bone, or visceral), clinical markers (prostate-specific antigen (PSA), alkaline phosphatase (ALP), hemoglobin (Hgb), albumin, LDH) before the initiation of enzalutamide or AA, HbA1c, LDL, HDL, triglycerides, within 2 months from the initiation of novel antiandrogen (AA or enzalutamide), treatment of diabetes (insulin, metformin or other oral agents), PFS on novel antiandrogens (AA or enzalutamide) and overall survival (from the initiation of the novel antiandrogens).

Statistical analysis

Simple linear regression analysis was used to predict the value of a continuous outcome based on the value of a predictor variable in our dataset. In extension to that, multiple regression analysis was used to predict the value of a continuous outcome based on the value of two or more predictors. All of the required assumptions were checked and confirmed before the use of each test and appropriate transformation of the values may apply. For each output in regression analysis, df stands for degrees of freedom, P for the statistical significance of the regression model, R^2 for the proportion of variance in the outcome that can be explained by the predictor, and the Coeff for the coefficient for the constant per independent variable (UCLA IDRE 2015*c*).

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Table 1 Patients, disease and treatment characteristics.

Characteristics	No	%
Median age (years)	69	
Range	61–77	
Treatment		
AA	36	59
Enzalutamide	25	41
Race		
White	22	36
African-American	39	64
Family history		
Diabetes	13	21
Cardiovascular disease	13	21
Prostate cancer	20	33
Social history		
Smoking	21	34
Alcohol abuse	11	18
Performance status (ECOG)		
0	19	31
1	30	49
2	9	15
3	2	3
4	1	2
Pain at baseline (faces pain rating scale 0–5)		
0	19	31
1	22	36
2	16	26
3	3	5
4	1	2
5	0	0
Comorbidities		
Cardiovascular disease	11	18
Cerebrovascular accidents	4	7
Congestive heart failure	4	7
Peripheral vascular disease	3	5
Dementia	2	3
COPD	0	0
Chronic kidney disease	10	16
Hemiplegia	0	0
Leukemia	1	2
Lymphoma	0	0
Other cancer	0	0
Liver disease	1	2
AIDS	0	0
CCI, mean (s.d.)	9.5 (1.5)	
Gleason score		
≤6	4	7
7	13	21
≥8	19	31
Unknown	25	41
Metastatic disease		
Lymph nodes	46	75
Bone	56	92
Visceral	4	5
Chemotherapy before AA or enzalutamide		
No	44	72
Yes	17	28
Clinical markers before the initiation of AA or enzalutamide, mean (s.d.)		
PSA (ng/mL)	172 (339)	
Alkaline phosphatase (IU/L)	254 (492)	
Hgb (mg/dL)	11.3 (1.6)	
Albumin (g/dL)	3.98 (0.35)	
LDH (U/L)	232.5 (71.6)	
Metabolic markers, mean (s.d.)		
HbA1c (%)	6.9 (1.6)	
HDL (mg/dL)	45 (12)	
LDL (mg/dL)	101.7 (36.7)	
Triglycerides (mg/dL)	145.3 (90.1)	

The one-way analysis of variance (ANOVA) was used to determine that there are significant differences between the means of independent groups. Two-way or factorial ANOVA was used to compare the mean differences between groups that have been split into two independent variables and assess the interaction between the two independent categorical variables on the continuous dependent variable. All of the required assumptions were checked and confirmed before the use of ANOVA and appropriate transformation of the values may apply. For each output in ANOVA, df stands for degrees of freedom, P for the statistical significance of the regression model, R^2 for the proportion of variance in the outcome that can be explained by the predictor, and the Coeff for the coefficient for the constant per independent variable (UCLA IDRE 2015*a*).

PFS is presented as mean value±s.d. Kaplan–Meier estimates were used to depict the difference in PFS stratified by groups with different HBA1c levels and log rank test was used to determine the statistical significance between these groups (UCLA IDRE 2015*b*). Stata v.13 and Excel 2013 were used as statistical software tool.

Results

Patients and outcomes

Sixty-one men with CRPC were included in this analysis. Of those, 36 were treated with AA and 25 with enzalutamide. The average PFS of our cohort was 8.3 months (±6.33 months). PFS on AA was 7.2±6.14 months and on enzalutamide was 9.9±6.39 months. As expected, overall survival rate was found to be predicted by the PFS demonstrating a positive linear relationship (df (1, 47), $P=0.0002$, $R^2=0.27$, coeff=0.38) confirming the common clinical practice which consists of changing the treatment agent upon disease progression. Patients and disease characteristics are summarized in Table 1.

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HbA1c and lipid profile as predictors of PFS

Thirty-eight patients were tested for HbA1c levels within 2 months before the initiation of treatment with novel antiandrogens and 36 were tested for LDL, 36 for HDL and 34 for triglycerides. We found that the HbA1c levels statistically significantly predicted adversely PFS (df (1.36), P=0.00, R^2=0.40, coeff=−3.28) (Fig. 1). On the contrary, LDL (df (1.35), P=0.07, R^2=0.12, coeff=0.03), HDL (df (1.35), P=0.64, R^2=0.06, coeff=0.002), and triglycerides (df (1.33), P=0.33, R^2=0.03, coeff=0.03) were not found to predict statistically significantly the PFS. In multiple regression model, all the above variables were simultaneously run and only HbA1c was found to be the statistically significant predictor (df_{model} (4.25), P_{model}=0.048, $R_{model}{}^2$=0.35, $coeff_{HbA1c}$=−1.46). The Kaplan–Meier analysis showed that there was significant difference in survival between the HbA1c 4.7–5.9% (first quartile of our available values) compared with patients with HbA1c 7.8–11.6% (fourth quartile of our available values) (6.72±1.3 months, log rank test P<0.0001) (Fig. 2). Breaking down the patients treated by each novel agent (either AA or enzalutamide), we found that in AA patients separately, HbA1c was also proven to be an adverse predictor for PFS (df (1.18), P<0.0001, R^2=0.65, coeff=−2.91) with a difference in survival of 4±1.01 months between AA patients with HbA1c within 4.7–5.9% compared with those with HbA1c within 7.8–11.6%.

BMI as a predictor of PFS

As a next step, we evaluated the potential contribution of BMI, which may interfere with HbA1c as a prognostic factor. In the multiple regression model consisting of HbA1c and BMI as predictors, only HbA1c contributed in the model significantly predicting PFS ((df_{model} (2.34), P_{model}=0.00, $R_{model}{}^2$=0.45, P<0.0001 for HbA1c with coeff=−2.86 and P=0.07 for BMI with coeff=0.028)). In addition to that, we performed full factorial ANOVA to assess the interaction between HbA1c and BMI and their effect on PFS and we confirmed that there is no statistical significance in their between association (P=0.73) and only HbA1c affected PFS. When we assessed BMI in a linear regression analysis as a single prognostic factor, we found that it can affect positively the PFS (df (1.59), P=0.02, R^2=0.09, coeff=0.01).

History, disease characteristics and associations with PFS

Based on our data, PFS on AA and enzalutamide does not differ significantly among the patients with a positive or negative family history of either diabetes (df (1.59), P=0.52, R^2=0.01), family history of PCa (df (1.59), P=0.57, R^2=0.01), or cardiovascular disease (df (1.59), P=0.22, R^2=0.03). Differences in age (df (1.59), P=0.09, R^2=0.05, coeff=0.003) and race (df (1.59), P=0.64, R^2=0.00, coeff=0.003) among our patients were not found to interfere with the PFS as well. Also, neither differences in smoking (df (1.59), P=0.4, R^2=0.01) nor in alcohol (df (1.59), P=0.40, R^2=0.01) habits among our patients were found to have any impact on PFS. Assessing the variability of the available Gleason scores, it did not impact on determining the PFS (df (1.35), P=0.94, R^2=0.00, coeff=0.00). Last but not least, previous treatment with

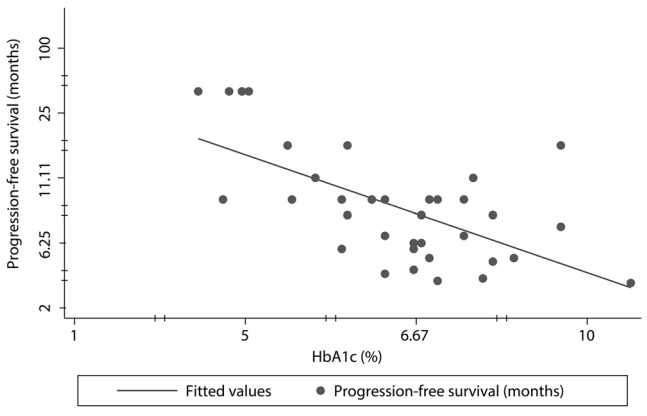

Figure 1
Linear regression analysis graph between progression-free survival on AA and enzalutamide and HbA1c.

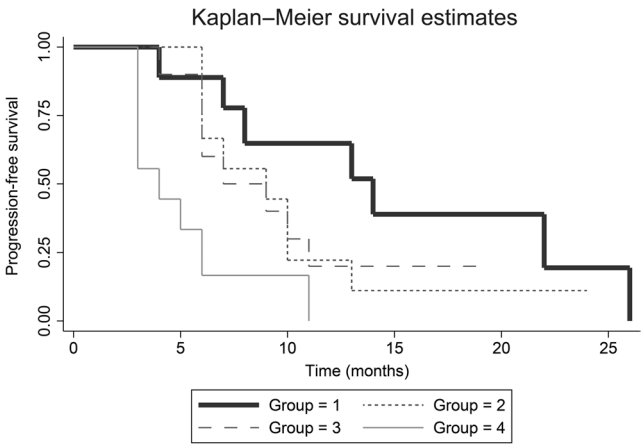

Figure 2
Kaplan–Meier progression-free survival estimates between HbA1c groups 1, 2, 3 and 4. HbA1c group 1 represents patients with values within 4.7–5.9%, group 2 within 6–6.6%, group 3 within 6.7–7.7% and group 4 within 7.8–11.6%. Log rank test revealed statistical difference in survival among groups 1 and 4 (P<0.0001).

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chemotherapy (docetaxel, cabazitaxel, Taxotere or their combinations) had no statistically significant input (P=1.00) in ANOVA model including PFS and HbA1c and no significant effect on their between interaction with HbA1c (P=0.32).

Associations of HbA1c with markers of overall sickness, poor health and poor prognosis

There was no association between HbA1c (dependent variable) and ECOG score (df (3.34), P=0.64, R^2=0.05), CCI score (df (5.32), P=0.51, R^2=0.12), level of pain (df (4.33), P=0.75, R^2=0.06), visceral metastases (df (1.36), P=0.92, R^2=0.00), bone metastasis (df (1.36), P=0.28, R^2=0.03), lymph node metastasis (df (1.36), P=0.15, R^2=0.06), cerebrovascular accidents (df (1.36), P=0.47, R^2=0.01), cardiovascular disease (df (1.36), P=0.18, R^2=0.05), congestive heart failure (df (1.536), P=0.88, R^2=0.00), peripheral vascular disease (df (1.36), P=0.52, R^2=0.01), chronic kidney disease (df (1.36), P=0.97, R^2=0.010), and leukemia (df (1.36), P=0.22, R^2=0.14). Presence of dementia, COPD, hemiplegia, lymphoma, other cancer, liver disease and AIDS did not apply on any patient. Regarding biochemical values, there was no association between HbA1c and PSA before treatment with novel antiandrogens (within 2 months) (df (1.36), P=0.26, R^2=0.04, coeff=0.00), LDH (df (1.2), P=0.24, R^2=0.58, coeff=0.01), albumin (df (1.31), P=0.47, R^2=0.02, coeff=0.01), and Hgb (df (1.36), P=0.06, R^2=0.10, coeff=0.01). HbA1c was found to be associated with ALP (df (1.35), P=0.01, R^2=0.26, coeff=2.85). The data are summarized in Table 2.

Table 2 Association of HbA1c with markers of overall sickness, poor health and poor prognosis.

Factors associated with overall sickness, poor health and poor prognosis	Association with HbA1c (P value)
Functional status – scores	
ECOG score	0.64
CCI score	0.51
Level of pain	0.75
Extent of disease	
Visceral metastases	0.92
Bone metastases	0.28
Lymph node metastases	0.15
Comorbidities	
Cerebrovascular accidents	0.47
Cardiovascular disease	0.18
Congestive heart failure	0.88
Peripheral vascular disease	0.52
Chronic kidney disease	0.97
Leukemia	0.22
Laboratory values	
PSA at baseline	0.26
LDH at baseline	0.24
Albumin at baseline	0.47
Hgb at baseline	0.06
ALP at baseline	0.01

Discussion

Although it is known that hyperglycemia and hyperlipidemia are associated with worse prognosis in numerous malignancies including PCa (Hammarsten & Hogstedt 2004, Ma *et al*. 2008), there are only limited data regarding their implications in the prognosis of CRPC patients and their response to novel antiandrogens. The latter would be particularly important given the lack of biomarkers that can predict the efficacy of these agents. In this observational study, we found that HbA1c levels predict adversely the PFS among patients treated with AA and enzalutamide. We showed that uncontrolled hyperglycemia with particularly elevated HbA1c (7.8–11.6%) led to mean difference of 7 months in PFS compared with patients with HbA1c 4.7–5.9%. LDL, HDL and triglycerides levels were not correlated with the PFS and BMI was found to predict but positively the PFS.

It is has been suggested that insulin resistance is associated with more advanced and aggressive PCa, while treatment with metformin reduces the risk of biochemical recurrence in patients with PCa (Raval *et al*. 2015). Mechanistically, insulin resistance is accompanied by hyperinsulinemia, which leads to the inhibition of insulin-like growth factor (IGF) binding protein and finally increase of IGF1 (Luo & Murphy 1992, Aggarwal *et al*. 2013). The latter activates the IGF axis, which serves as a growth signaling in PCa cells (Winters *et al*. 2015). Consistently, diabetes at the time of PCa diagnosis is associated with higher grade and stage, increased incidence of recurrence, and shorter time to CRPC (Hammarsten & Hogstedt 2005, Ma *et al*. 2008, Flanagan *et al*. 2011).

Despite this well-documented association between diabetes and PCa progression, there are scarce aggregate data regarding the implications of diabetes in the state of castration-resistance and response to novel antiandrogens. We found that HbA1c levels predict adversely the PFS on AA and enzalutamide, decreasing the survival by approximately 7 months. To our knowledge, this finding is novel and provides substantial information for CRPC patients. Recently, Antonarakis *et al*. (2014) demonstrated that the detection of AR splice variant 7 messenger (AR-V7) RNA in circulating tumor cells from

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patients with metastatic PCa could predict poor response to novel antiandrogens and worse survival. Similarly, HbA1c is an easily checked blood marker, which, according to our findings, may also predict resistance to novel antiandrogens. Maybe, thanks to its modifiable potential, it can add significantly on the efficient patients' management. Further research is warranted to assess the degree of impact of long-standing compared with short-term diabetes on PFS. Also, analysis of larger databases and prospective case–control studies are required to further assess the causal association between diabetes control and PFS on AA or enzalutamide and explore if any substantial difference exists between controlled and uncontrolled diabetes and survival.

Of note, no difference was found between PFS and potentially interfering factors with our conclusions such as age, race, social history and family history of diabetes, PCa and cardiovascular disease, since these factors have been associated with uncontrolled diabetes. Remarkably, previous chemotherapy regimens among patients did not interact significantly with HbA1c levels. This highlights the potential direct correlation between HbA1c and response to novel agents, since PFS and overall survival on AA and enzalutamide chemotherapy in previously treated patients has been confirmed to be shorter compared with chemotherapy-naïve patients (de Bono *et al*. 2011, Scher *et al*. 2012, Ryan *et al*. 2015). Finally, given that uncontrolled diabetes may represent general sickness, we investigated and found no correlation between HbA1c and factors associated with overall illness and compromised performance such as ECOG performance status, CCI score, level of pain, presence of visceral, lymph nodes, and bone metastases, a variety of comorbidities, and PSA and Hgb levels. Based on our data, HbA1c is significantly associated with the ALP levels before the initiation of AA or enzalutamide. Although high ALP levels suggest existence of liver or, mainly, bone metastases with or without excessive activity, we did not find any correlation between the presence of either bone or visceral metastases with HbA1c levels. Surprisingly, ALP has been also linked with the calcification of arteries in the light of metabolic syndrome having been used as a marker for that (Cheung *et al*. 2013). Further investigation of this finding is needed, but it is beyond of the purpose of this study.

Although we found that HbA1c affected PFS of patients on AA and enzalutamide, collectively, we noticed that if we break down the patients per agent, the effect remained significant only for the AA patients. However, enzalutamide patients did have a similar trend but not statistically significant, an observation that could be explained by the smaller sample or other hypotheses. It may imply a different mechanism of hyperglycemia implication based on the difference of pharmacokinetics or mechanism of activity between these agents. Further studies are needed to clarify the different effects of uncontrolled diabetes on the response to the novel antiandrogens. Based on our findings, diabetic patients with CRPC on AA should be monitored enough to achieve adequate control of their diabetes. Taken into consideration that these patients are also started on prednisone (de Bono *et al*. 2011), it can render the control of diabetes particularly challenging.

Similarly, numerous studies have highlighted the role of hyperlipidemia as inducer of cancer aggressiveness (Bhindi *et al*. 2015). In our analysis, no correlation was found between the PFS on AA and enzalutamide and lipid profile of CRPC patients. On the contrary, we demonstrated that BMI was positively associated with the PFS on AA and enzalutamide. It has been previously shown that obesity and elevated BMI at the PCa diagnosis are associated with worse prognosis (Ma *et al*. 2008, Komaru *et al*. 2010). However, Halabi *et al*. (2007) demonstrated that obesity was associated with decreased risk of cancer-specific mortality in patients with CRPC thought to be associated with cancer cachexia at this stage of disease. It is well established that cancer-associated cachexia is related not only to worse quality of life, but also to definite deterioration of survival rates (Vaughan *et al*. 2013). This conclusion is consistent with our findings, which further support that probably elevated BMI is associated with improved response to novel agents and survival for patients with CRPC. Further research should be conducted on determining the appropriate BMI range, which corresponds to better survival outcome.

Conteduca *et al*. (2015) recently found that patients with metabolic syndrome had shorter PFS on AA treatment without effect on overall survival. According to these data, it remains unclear if obesity or alterations in glucose and lipid metabolism are implicated in the prognosis of patients with CRPC and specifically in the response to the novel agents. According to our findings, uncontrolled diabetes is the crucial factor determining the response to novel antiandrogens and subsequently the prognosis of patients with CRPC. Indeed, Lee *et al*. (2012) showed that diabetes increased the risk of PCa development independently of hyperlipidemia. Thus, it can be hypothesized that hyperglycemia may be the confounding factor between metabolic syndrome and

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PFS on novel antiandrogens and the metabolic alteration, which truly predicts the outcome.

In conclusion, we demonstrated that uncontrolled diabetes predicts for poor response to novel antiandrogens, whereas we could not find any relevant association with hyperlipidemia. We also showed that BMI was positively associated with the response to novel antiandrogens. Further studies are needed to establish these associations and clarify the underlying pathophysiology.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

T K and G G conceptualized and designed the study, participated in data collection, extraction and interpretation. T K, S K and G G wrote and drafted the manuscript, approved the final manuscript as submitted, and agreed to be accountable for all aspects of the work related to the accuracy or integrity of any part of the work appropriately investigated and resolved. T K and S K performed the statistical analysis and prepared tables and figures.

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