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Platinum Opinion

Repurposing Metformin as Therapy for Prostate Cancer within the STAMPEDE Trial Platform

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1. Rationale for evaluating metformin

The current standard-of-care (SOC) for men presenting with high-risk locally advanced or metastatic prostate cancer (CaP) includes long-term androgen deprivation therapy (ADT), a treatment associated with metabolic dysfunction, including insulin resistance, hyperglycaemia, and obesity. More than 50% of men who receive long-term ADT develop a form of metabolic syndrome, which can potentially increase their risk of cardiovascular morbidity and mortality [1]. The median overall survival for this patient population is now almost 6 yr. The need to mitigate the debilitating effects of prolonged ADT is increasingly relevant.

Metformin has proven benefit in this setting. In nondiabetic patients, metformin reduces the incidence of diabetes and the adverse metabolic effects of ADT, including hyperinsulinaemia and dyslipidaemia [2]. In diabetic patients, metformin decreases myocardial infarction risk and prolongs survival [3].

These effects may be explained by the activation of AMPK, which inhibits fatty acid synthesis and thus reduces levels of cholesterol, low-density lipoproteins, and triglycerides. Metformin also decreases platelet-aggregation factor 1, other vascular adhesion molecules, and C-reactive protein [4,5]. Metformin has antineoplastic properties, possibly explained by preclinical data showing that cancer progression is integrally linked to metabolic modulators [6]. Modification of this process by metformin has the potential to impact on CaP-specific survival [7,8].

Metformin reduces hyperinsulinaemia, a condition that promotes cancer metastasis, growth, and treatment resistance [9]. In CaP models, insulin increases mRNA and protein expression of steroidogenic enzymes, upregulating intracellular testosterone levels and androgen receptor (AR) activation [10]. By reducing hyperinsulinaemia, metformin can influence multiple other cancer pathways, including insulin-like growth factor (IGF) and PI3K-AKT/AR signalling, both of which are associated with CaP progression and castrate resistance. Metformin also exerts an antiproliferative effect via inhibition of mTOR and may target cancer stem cells and epithelial-to-mesenchymal transition, thereby inhibiting metastatic progression [11,12].

Cancer outcomes in diabetic men receiving metformin provide epidemiologic evidence of an anticancer effect. A meta-analysis of 9186 men with diabetes and CaP showed that metformin decreased biochemical recurrence and improved overall survival [13].

In response to preclinical, clinical, and epidemiologic evidence of an anticancer effect, trials are now evaluating metformin in lung, breast, pancreatic, and ovarian cancer. Encouraging nonrandomised phase 2 data for castrate-resistant CaP demonstrated that 36% of patients treated with metformin were progression-free at 3 mo. When compared to baseline values, the prostate-specific antigen (PSA) doubling time was prolonged in 52% of cases, and an overall clinical benefit was observed in 46% [14,15]. Ongoing trials in CaP include the Metformin Active Surveillance Trial (MAST), recruiting men with low-risk CaP (NCT01864096), and trials

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† Members of the STAMPEDE Trial Management Group are listed in Appendix A.

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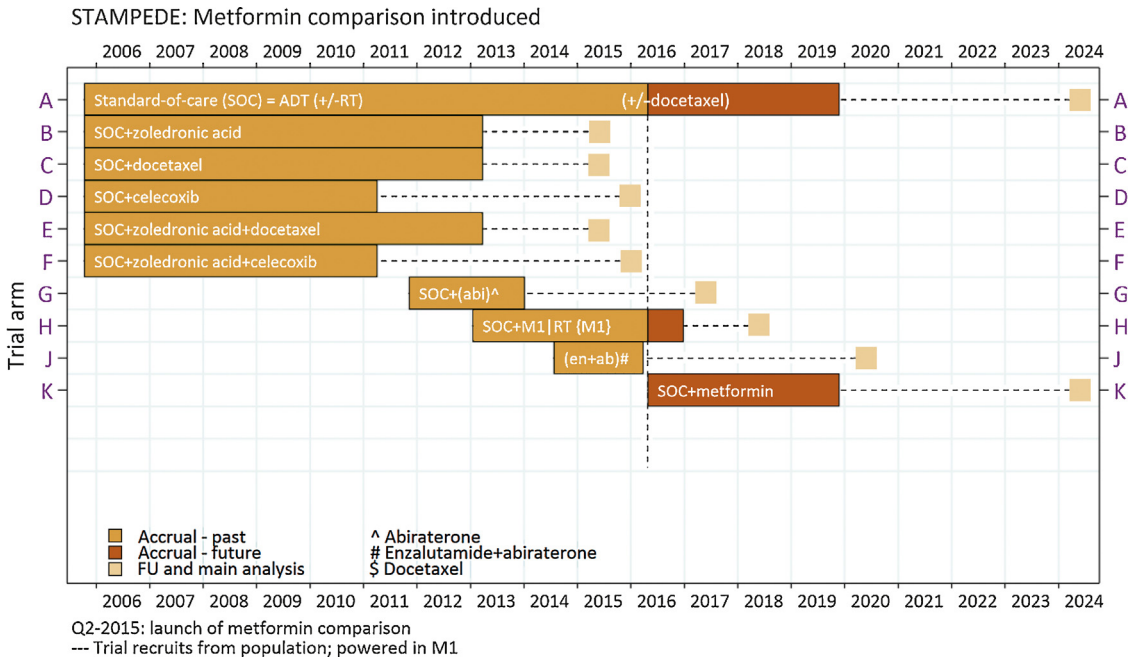

Fig. 1 – STAMPEDE accrual activity over time. ADT = androgen deprivation therapy; RT = radiotherapy; FU = follow-up.

adding metformin to abiraterone or docetaxel in the castrate-resistant setting (NCT01796028, NCT01677897). To the best of our knowledge, there are no ongoing or planned trials that will evaluate metformin among men with high-risk locally advanced or metastatic CaP newly commencing long-term ADT.

2. Evaluating metformin in the STAMPEDE trial

The ongoing STAMPEDE trial evaluates whether adding therapies to the SOC improves survival among men with high-risk localised or metastatic (M1) CaP. By June 2016, more than 8000 consenting men at >100 centres in the UK and Switzerland had joined the trial platform, which will use a multiarm, multistage (MAMS) design for nine randomised comparisons (Fig. 1). STAMPEDE is in a unique position to address two new and important questions: can the anti-diabetic drug metformin be repurposed to mitigate ADT-related metabolic dysfunction and can it improve survival in CaP patients?

The metformin comparison will compare SOC plus metformin (new research arm K) to the current SOC (control arm A). For inclusion, men must be nondiabetic (glycated haemoglobin A1c [HbA1c] <6.5%, equivalent to <48 mmol/ml) and meet a more stringent renal cutoff than currently used in the trial (creatinine clearance >60 ml/min). Allocation will be 1:1 to the control arm or research arm K. Currently, eligible patients newly diagnosed with M1 disease can also be allocated to receive prostate radiotherapy (arm H). Future MAMS trial principles for the metformin comparison are different from hitherto: overall survival will be used as both the intermediate and definitive primary outcome measure. Failure-free survival (used in other comparisons as the intermediate primary outcome measure) is driven predominantly by PSA failure and therefore was judged not to be appropriate in determining metformin benefit. The drug will be continued throughout long-term ADT and past the FFS event. Approximately 1800 patients will be required (including approximately 1200 with metastatic disease) to achieve 85% power to detect a 20% relative improvement in overall survival at the final efficacy stage. Metabolic parameters evaluated will include body mass index, HbA1c, fasting glucose and lipid profiles, and any new manifestation of cardiovascular disease or diabetes mellitus.

3. Challenges and considerations

3.1. *Tolerability*

Metformin is well tolerated, and ongoing trials evaluating its use in men without diabetes report low discontinuation rates due to toxicity (~4%). Lactic acidosis, the most serious toxicity, is very rare and may be caused by underlying diabetes rather than metformin treatment. This is supported by a meta-analysis demonstrating comparable rates of lactic acidosis between untreated diabetic patients and those treated with metformin [16].

3.2. *Optimal treatment duration*

Metformin can be safely added to other treatments currently used in CaP; as several of these involve co-prescribed steroids, addition of metformin may help to counteract steroid-induced hyperglycaemia. Metformin will be continued alongside long-term ADT and given in

addition to all subsequent treatments. Men with M0 disease at trial entry will receive metformin for 3 yr after randomisation or until 12 mo after last administration of a luteinising hormone–releasing hormone analogue, whichever is longer. Men with M1 disease will have lifelong therapy provided it is tolerated and safe. The long-term duration of metformin administration for anticancer testing is guided by epidemiologic evidence showing that it reduces the risk of CaP progression when it is given for ≥3 yr [17].

3.3. *Feasibility*

As a generic, low-cost drug, if shown to be beneficial, metformin could have an impact in both high- and low-resource health systems. Taken together with its low toxicity profile, this means that a smaller relative improvement is likely to be clinically significant. However, the absence of industry support means that the acquisition of data depends on academic-led studies, which are required to be large to have the sufficient power to detect a smaller difference. Trial platforms such as STAMPEDE that evaluate multiple therapeutic approaches can attract both industry and charitable support and accrue at a sufficient rate necessary to address these globally important questions on a feasible timescale.

4. Conclusions

Metformin is a safe, well-tolerated, inexpensive treatment that can be given in addition to current SOC therapies for CaP. Its use might mitigate the deleterious side effects of castration and exert an additional anticancer effect. It is under investigation in multiple tumour types and with the support of the investigators, patients, and funders (Cancer Research UK and the UK Medical Research Council) it will be incorporated in the STAMPEDE trial platform in summer 2016. This will test its true utility as a repurposed treatment for men with high-risk locally advanced or metastatic CaP at first presentation.

STAMPEDE is registered on ClinicalTrials.gov as NCT00268476.

Conflicts of interest: The authors have nothing to disclose.

Appendix A. Members of the STAMPEDE Trial Management Group

Clinical members: Nick James, Gerhardt Attard, Noel Clarke, Bill Cross, David Dearnaley, Silke Gillessen, Clare Gilson, Rob Jones, Malcolm Mason, Chris Parker, Alastair Ritchie, Martin Russell, George Thalmann.

Statistical members: Mahesh Parmar, Melissa Spears, Matthew Sydes.

Patient members: Robin Millman, David Matheson.

Trial and data management members: Claire Amos, Nargis Begum, Clare Gilson, Claire, Murphy, Orla Prendiville, Francesca Schiavone, Melissa Spears, Matthew Sydes, Carly Au, Peter Vaughan, Zohrah Khan, Estelle Cassoly.

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