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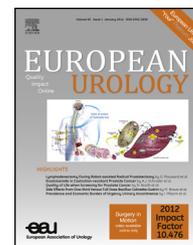
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European Association of Urology



## Platinum Opinion

# Combining Enzalutamide with Abiraterone, Prednisone, and Androgen Deprivation Therapy in the STAMPEDE Trial

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## 1. The STAMPEDE trial

STAMPEDE (ClinicalTrials.gov identifier NCT00268476) is a flagship multiarm, multistage, open-label, randomised controlled trial in the United Kingdom and Switzerland evaluating the combination of novel treatment strategies with androgen deprivation therapy (ADT). This includes assessing whether effective second-line treatments should be used for patients commencing long-term ADT for the first time. The trial launched in October 2005 with five research arms compared pairwise against a common control arm (Fig. 1), and to date, >5500 men have been recruited. The celecoxib arms were closed for lack of sufficient activity at the second preplanned interim analysis [1]. The remaining original arms—zoledronic acid, docetaxel, and zoledronic acid with docetaxel—successfully recruited throughout all interim stages and closed to recruitment in March 2013. Primary outcome data from these original arms are expected in mid-2015.

Introducing a new research arm within the novel multiarm adaptive design of STAMPEDE, rather than a separate, competing trial, is an efficient approach with immediate start-up at >100 sites and the use of a shared control arm that will give answers more quickly without adversely affecting the timelines for the ongoing comparisons. A new

arm (arm G) of abiraterone, prednisone, and ADT was seamlessly introduced in November 2011 (Fig. 1), and accrual of >1900 patients to this randomised comparison of abiraterone was completed in January 2014. A new arm (arm H) considering radiotherapy (RT) to the prostate for newly diagnosed metastatic patients was introduced in January 2013 [2]. Now another new arm (arm J), combining enzalutamide, abiraterone, and prednisone with ADT, is being initiated in July 2014 throughout the United Kingdom.

## 2. Rationale for CYP17A1 inhibition in hormone-sensitive disease

ADT with luteinising hormone-releasing hormone analogues reduces the total androgen pool by up to 80% in a 60-yr-old man [3]. Abiraterone is a specific CYP17A1 inhibitor that effectively suppresses nongonadal androgen and oestrogen synthesis [3]. Treatment of noncastrate men with abiraterone is associated with an initial decrease in serum testosterone, but a subsequent surge in luteinising hormone causes an increase in gonadal androgen synthesis that is not inhibited by currently approved doses of abiraterone [4]. Consequently, men receiving abiraterone 1000 mg daily require concomitant effective inhibition of gonadal steroidogenesis. Due to the inhibition of both

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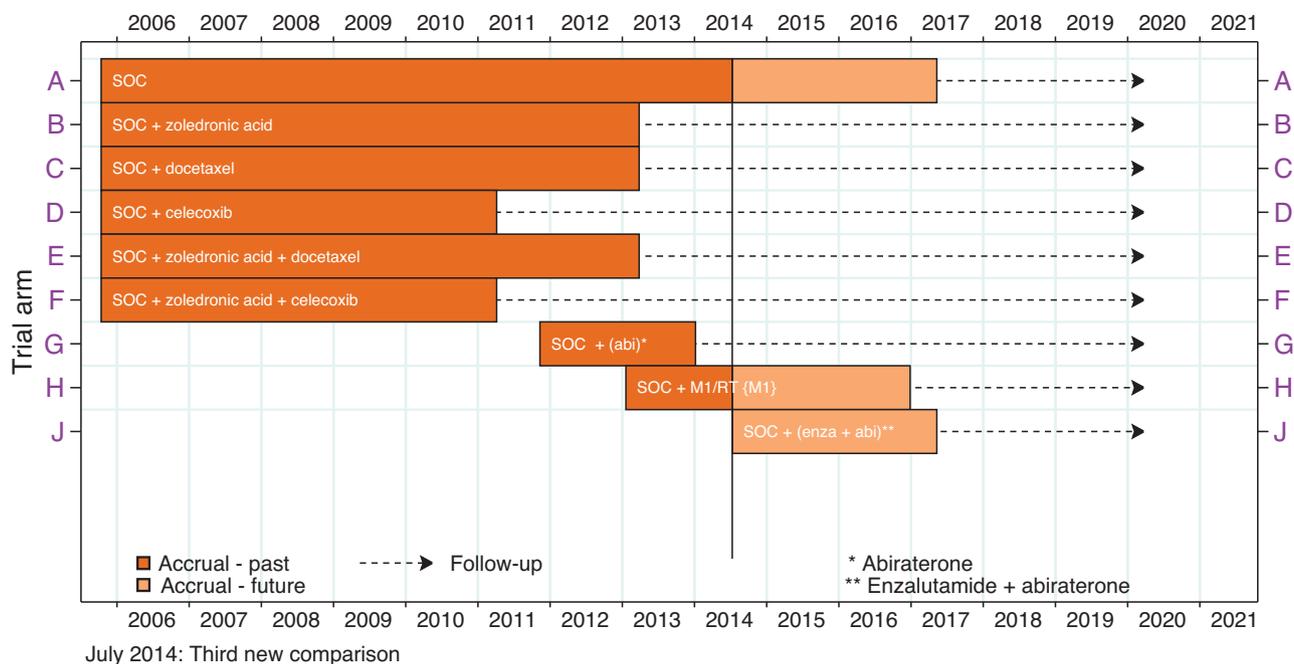


Fig. 1 – Accrual activity over time.

SOC = Standard-of-care = ADT (+/–RT); ADT = androgen deprivation therapy; RT = radiotherapy.

CYP17A1 C17,20-lyase and 17 $\alpha$ -hydroxylase, treatment with abiraterone is associated with inhibition of cortisol synthesis and a consequent rise in adrenocorticotrophic hormone, which is associated with a syndrome of secondary mineralocorticoid excess in up to 90% of patients [3]. Abiraterone has thus been developed for the treatment of metastatic castration-resistant prostate cancer (CRPC) in combination with prednisone or prednisolone [5].

Clinical trials demonstrating the efficacy of abiraterone in CRPC have confirmed that a significant proportion of tumours are dependent on sex steroids that persist despite castration [5]. In addition to suppression of circulating androgens and oestrogens, abiraterone could also inhibit CYP17A1-dependent androgen synthesis by the cancer itself, although this is harder to prove and remains speculative. In addition, abiraterone is a weak antagonist of the androgen receptor (AR) [6], although the clinical relevance of this remains uncertain. In the newly diagnosed patients with M1 disease in the control arm of STAMPEDE, the median time to progression on castration is 12 mo [7]. Consequently, there is a clear need for treatments in addition to ADT in a high-risk population. Potential mechanisms of castration resistance that will be targeted by combination with abiraterone include activation of AR signalling by residual low levels of androgens and CYP17A1 tumoural androgen synthesis.

### 3. Rationale for combined castration, CYP17A1 inhibition, and androgen receptor antagonism in hormone-sensitive disease

Enzalutamide is a rationally designed AR antagonist that is effective in men with CRPC, including in those patients who

have progressed on bicalutamide [8]. Enzalutamide is very well tolerated, and other than side effects related to profound androgen suppression, there is no evidence of overlapping side effects between abiraterone with prednisone or prednisone and enzalutamide. The combination of these agents is undergoing evaluation in a single-arm phase 1b clinical trial in metastatic CRPC at MD Anderson Cancer Center (ClinicalTrials.gov identifier NCT01650194), and preliminary data suggest no increased toxicity. The efficacy of the combination of abiraterone, prednisone, and enzalutamide is being compared with enzalutamide alone in chemotherapy-naïve metastatic CRPC, with overall survival as the primary outcome measure (ClinicalTrials.gov identifier NCT01949337). An industry-sponsored randomised trial is also evaluating radiologic progression-free survival of enzalutamide in combination with abiraterone and prednisolone compared with placebo, abiraterone, and prednisone in patients with CRPC and rising prostate-specific antigen on enzalutamide (ClinicalTrials.gov identifier NCT01995513).

Translational studies suggest increased androgen synthesis in patients treated with enzalutamide [9] that could result in “outcompeting” of enzalutamide at the AR [6]. This would be inhibited by combining enzalutamide with abiraterone. Conversely, abiraterone does not completely suppress steroids that could activate a “hypersensitive” or “promiscuous” AR; this mechanism for maintained AR activation could be inhibited by combination with enzalutamide. Consequently, there is a pressing case for agents from these classes to be assessed synchronously for activity and synergism in hormone-naïve disease.

#### 4. Concerns with triple-combination therapy

Although there is the potential for greater activity in these patients, there may be issues of toxicity or practical use of the combination that limit any advantage.

##### 4.1. Long-term metabolic toxicity associated with more profound androgen suppression and concomitant glucocorticoid administration

Limited data are available on the long-term side effects associated with metabolic disturbances from novel endocrine agents, although the sequelae of castration are well described and could be worsened by longer use of additional endocrine treatments.

##### 4.2. Priming of cancers to earlier development of resistance

The mechanisms of resistance to abiraterone and enzalutamide are still being elucidated. Recently, a point mutation in the AR was described that results in activation rather than antagonism of AR signalling by enzalutamide [10]. Similarly, activation of the AR by glucocorticoids following development of AR point mutations can occur [6]. Both agents target ligand activation of the AR and thus could share mechanisms of resistance, including, for example, an increase in constitutively active AR splice variants that lack the ligand binding domain and upregulation of the glucocorticoid receptor that maintains expression of steroid receptor-regulated genes [11]. The use of these treatments in hormone-sensitive disease could prolong failure-free survival but also “prime” the disease to earlier development of resistance with later AR-targeting strategies, leading to a failure to affect overall survival.

##### 4.3. Cost

The UK list price of abiraterone is approximately £2630, with independent estimates of cost per quality-adjusted life-year equivalent to £46,800–50,000 [12]. The list price of enzalutamide is currently more (approximately £3500). Consequently, combination therapy may be prohibitively expensive but will decrease, perhaps around the time our data mature.

#### 5. Trial design considerations

Overall, 1800 patients will be randomised 1:1 to the control arm (currently ADT with additional prostate RT for NOMO patients) or to research arm J. Patients with newly diagnosed metastatic disease may instead be allocated to a third arm (arm H) assessing the role of RT to the prostate (Fig. 1) [2]. Two intermediate analyses of lack of sufficient activity based on failure-free survival will be undertaken and reviewed by the Independent Data Monitoring Committee (IDMC) in line with the ongoing trial design. The IDMC will also assess toxicity, with the first review planned after 50 patients have been allocated to arm J and have been on trial for just 6 wk; a further review will take place when

50 patients in arm J have been on trial for approximately 6 mo. Recruitment will take up to 3 yr, with reporting of overall survival predicted for approximately 3 yr later (approximately 2020). An indirect comparison of the relative efficacy of adding enzalutamide to abiraterone will be possible through the published results of the separate STAMPEDE “abiraterone comparison” (arm G); however, the converse indirect comparison would require network meta-analysis with relevant trials assessing addition of enzalutamide to ADT.

#### 6. Conclusions

The introduction of the new arm J has received the support of investigators, patients, funders (Cancer Research UK and the Medical Research Council), and pharmaceutical partners (including Astellas and Janssen). The efficiencies engendered by undertaking this comparison as an amendment to the multiarm, multistage STAMPEDE trial should facilitate rapid answers to the questions posed by use of this novel combination.

**Conflicts of interest:** Gerhardt Attard, Johann S. de Bono, David P. Dearnaley, and Chris C. Parker are affiliated with the Institute of Cancer Research (ICR), which has a financial interest in abiraterone. Gerhardt Attard has received consulting fees and travel support from Astellas, Janssen, and Medivation and is included in the ICR rewards to inventors for abiraterone. Noel W. Clarke has undertaken consultancy work both for Astellas and Janssen, has given lectures at symposia organised by them, and has received honoraria. Johann S. De Bono has served on Astellas advisory boards as a paid consultant. David P. Dearnaley has served on advisory boards and participated in meetings for Astellas. Nicholas D. James has served on advisory boards and lectured for Astellas. Malcolm D. Mason has served on advisory boards for and received honoraria from Astellas. Chris C. Parker has been a speaker for and received honoraria from Astellas. The other authors have nothing to disclose.

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