Shamash J, Powles T, Sarker SJ, Protheroe A, Mithal N, Mills R, Beard R, Wilson P, Tranter N, O'Brien N, McFaul S, Oliver T (2011) A multi-centre randomised phase III trial of Dexamethasone vs Dexamethasone and diethylstilbestrol in castration-resistant prostate cancer: immediate vs deferred Diethylstilbestrol. *Br J Cancer* **104**: 620–628.

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Reply: 'Comment on Anti-tumour activity of abiraterone and diethylstilboestrol when administered sequentially to men with castration-resistant prostate cancer'

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Sir,

We thank Shamash and Sarker for their interest in our recent article (Omlin *et al*, 2013). They make three comments: first, that the activity of diethylstilboestrol (DES) when combined with a corticosteroid such as dexamethasone (D) is increased compared to DES alone; second, that chemotherapy may re-induce sensitivity to a hormonal agent; finally, their experience in 11 patients who received the sequence of docetaxel followed by DES and D and then abiraterone acetate (AA) and prednisone. In this setting the activity of AA was limited, as indicated by a median progression-free survival (PFS) of 1.8 months (range 0.6–8.1).

We wish to clarify that we did not report any data on DES activity prior to treatment with AA because it was not possible to get complete DES activity data for patients treated outside of our institution. We therefore only reported duration of DES treatment. Our large institutional experience with single-agent DES and aspirin in 231 men with castration resistant prostate cancer (CRPC) showed a median time to PSA progression of 4.6 months, $\geqslant$50% PSA declines in 28.9% of patients and a VTE rate of 9.9% (Wilkins *et al*, 2012). We acknowledge that the activity of DES may be modestly higher when it is combined with D, which has been shown to have single-agent anti-tumour activity in men with castration-resistant prostate cancer, although there is little evidence that this therapeutic manoeuvre imparts significant clinical benefit (Venkitaraman *et al*, 2008). The comparison of DES plus D with D alone by Shamash *et al* (2011) is interesting but raised concerns that DES is associated with a major risk of serious toxicity, unlike AA, with veno-thromboembolic events (VTEs) in 22% of patients despite prophylactic treatment with aspirin. Given that AA provides overall survival benefit in Phase III trials, AA is a preferable treatment to DES for CRPC (de Bono *et al*, 2011; Ryan *et al*, 2013). Indeed we believe that there may now be little merit in administering DES to patients suffering from CRPC.

The hypothesis that chemotherapy may induce sensitivity to endocrine agents is also intriguing. However, clinical trials of AA and enzalutamide have all reported higher response rates pre-chemotherapy than afterwards, suggesting overlapping mechanisms of resistance (Scher *et al*, 2010, 2012; de Bono *et al*, 2011; Ryan *et al*, 2013). The study referenced by Shamash *et al* (2008) did not utilise taxanes (that through their postulated disruption of AR signalling may be associated with cross-resistance with endocrine treatments) and allowed cessation of androgen deprivation with 49% of patients having non-castrate levels of testosterone at the

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completion of chemotherapy (Shamash *et al*, 2008). The responses observed could therefore be related to re-initiation of castration. Nevertheless, we too envision that in the future we will be able to interrogate the evolution – emergence, disappearance and possibly re-emergence – of different CRPC clones/sub-clones following different therapeutic pressures. We believe that the pursuit of translational studies of circulating biomarkers and CRPC tissue urgently need to be prioritised to address these issues.

Finally, Shamash *et al* (2008) report minimal activity in 11 patients who received AA after docetaxel followed by DES given with D. Recently published case series have similarly indicated that the activity of AA is reduced when administered after docetaxel and enzalutamide (Loriot *et al*, 2013; Noonan *et al*, 2013). Our report observed PSA declines $\geqslant$50% in 28.4% of 81 patients treated with AA after DES and docetaxel and radiological responses in 25% of patients (Omlin *et al*, 2013). The differences of these two reports could be explained by the *post hoc* nature of the analyses and the differences in use of steroids. As AA is now commonly used pre-chemotherapy and prior to DES, the latter is often an option of last resort. Overall, however, our report indicates that the limited activity and the significant toxicity of DES should limit its use in patients who have previously progressed on AA and docetaxel, and that patients should be offered agents with a proven survival benefit or clinical trials in this situation.

CONFLICT OF INTEREST

Abiraterone acetate was developed at The Institute of Cancer Research, which therefore has a commercial interest in the development of this agent. CP received lecture fees from Sanofi-Aventis and travel support from Sanofi-Aventis and Janssen-Cilag. DD received honoraria for advisory boards and served as a consultant for Takeda, Amgen, Astellas Pharma and Succinct Healthcare. JSdB received consulting fees from Ortho Biotech Oncology Research and Development (a unit of Cougar Biotechnology), consulting fees and travel support from Amgen, Astellas, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Dendreon, Enzon, Exelixis, Genentech, GlaxoSmithKline, Medivation, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, Supergen and Takeda, and grant support from AstraZeneca and Genentech. GA received consulting fees and travel support from Janssen-Cilag, Veridex, Roche/Ventana and Millennium Pharmaceuticals, lecture fees from Janssen-Cilag, Ipsen, Takeda and Sanofi-Aventis and grant support from AstraZeneca and Genentech. GA and DD are on The ICR rewards to inventors list of abiraterone acetate.

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