Abiraterone acetate plus prednisolone with or without enzalutamide for patients with metastatic prostate cancer starting androgen deprivation therapy: final results from two randomised phase 3 trials of the STAMPEDE platform protocol

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BACKGROUND

Abiraterone acetate plus prednisolone (herein referred to as abiraterone) or enzalutamide added at the start of androgen deprivation therapy improves outcomes for patients with metastatic prostate cancer. Here, we aimed to evaluate long-term outcomes and test whether combining enzalutamide with abiraterone and androgen deprivation therapy improves survival.

METHODS

We analysed two open-label, randomised, controlled, phase 3 trials of the STAMPEDE platform protocol, with no overlapping controls, conducted at 117 sites in the UK and Switzerland. Eligible patients (no age restriction) had metastatic, histologically-confirmed prostate adenocarcinoma; a WHO performance status of 0-2; and adequate haematological, renal, and liver function. Patients were randomly assigned (1:1) using a computerised algorithm and a minimisation technique to either standard of care (androgen deprivation therapy; docetaxel 75 mg/m2 intravenously for six cycles with prednisolone 10 mg orally once per day allowed from Dec 17, 2015) or standard of care plus abiraterone acetate 1000 mg and prednisolone 5 mg (in the abiraterone trial) orally or abiraterone acetate and prednisolone plus enzalutamide 160 mg orally once a day (in the abiraterone and enzalutamide trial). Patients were stratified by centre, age, WHO performance status, type of androgen deprivation therapy, use of aspirin or non-steroidal anti-inflammatory drugs, pelvic nodal status, planned radiotherapy, and planned docetaxel use. The primary outcome was overall survival assessed in the intention-to-treat population. Safety was assessed in all patients who started treatment. A fixed-effects meta-analysis of individual patient data was used to compare differences in survival between the two trials. STAMPEDE is registered with ClinicalTrials.gov (NCT00268476) and ISRCTN (ISRCTN78818544).

FINDINGS

Between Nov 15, 2011, and Jan 17, 2014, 1003 patients were randomly assigned to standard of care (n=502) or standard of care plus abiraterone (n=501) in the abiraterone trial. Between July 29, 2014, and March 31, 2016, 916 patients were randomly assigned to standard of care (n=454) or standard of care plus abiraterone and enzalutamide (n=462) in the abiraterone and enzalutamide trial. Median follow-up was 96 months (IQR 86-107) in the abiraterone trial and 72 months (61-74) in the abiraterone and enzalutamide trial. In the abiraterone trial, median overall survival was 76·6 months (95% CI 67·8-86·9) in the abiraterone group versus 45·7 months (41·6-52·0) in the standard of care group (hazard ratio [HR] 0·62 [95% CI 0·53-0·73]; p<0·0001). In the abiraterone and enzalutamide trial, median overall survival was 73·1 months (61·9-81·3) in the abiraterone and enzalutamide group versus 51·8 months (45·3-59·0) in the standard of care group (HR 0·65 [0·55-0·77]; p<0·0001). We found no difference in the treatment effect between these two trials (interaction HR 1·05 [0·83-1·32]; pinteraction=0·71) or between-trial heterogeneity (I2 p=0·70). In the first 5 years of treatment, grade 3-5 toxic effects were higher when abiraterone was added to standard of care (271 [54%] of 498 vs 192 [38%] of 502 with standard of care) and the highest toxic effects were seen when abiraterone and enzalutamide were added to standard of care (302 [68%] of 445 vs 204 [45%] of 454 with standard of care). Cardiac causes were the most common cause of death due to adverse events (five [1%] with standard of care plus abiraterone and enzalutamide [two attributed to treatment] and one (<1%) with standard of care in the abiraterone trial).

INTERPRETATION

Enzalutamide and abiraterone should not be combined for patients with prostate cancer starting long-term androgen deprivation therapy. Clinically important improvements in survival from addition of abiraterone to androgen deprivation therapy are maintained for longer than 7 years.