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Title: Fulvestrant 500 mg versus anastrozole as first-line treatment for advanced breast cancer: overall survival from the phase II 'first' study

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Body: Background: Fulvestrant 500 mg showed a clinically significant improvement in median overall survival (OS) vs fulvestrant 250 mg (26.4 vs 22.3 months, respectively; hazard ratio [HR] 0.81; 95% confidence interval (CI) 0.69, 0.96; nominal p=0.02) in the Phase III CONFIRM study, for patients (pts) with hormone receptor positive (HR+) disease following failure on prior endocrine therapy. Further evidence for OS effects of fulvestrant 500 mg was sought in the Fulvestrant fIRst-line Study comparing endocrine Treatments (FIRST), which compared fulvestrant 500 mg with anastrozole as first-line treatment for postmenopausal pts with HR+ locally advanced (LA) or metastatic breast cancer (MBC). In the primary analysis, fulvestrant 500 mg was as effective as anastrozole for clinical benefit rate (primary endpoint) and significantly better for time to progression (TTP; secondary endpoint). In a follow-up analysis, median TTP was 23.4 months for fulvestrant 500 mg vs 13.1 months for anastrozole (HR 0.66; 95% CI 0.47, 0.92; p=0.01). Here we report the only scheduled FIRST OS analysis.
Methods: FIRST, a Phase II, randomized, open-label study (NCT00274469), compared fulvestrant 500 mg (im on Days 0, 14 and 28, and every 28 days thereafter) with anastrozole (1 mg/day po). Pts had not received prior endocrine therapy for advanced disease. OS (time from randomization to death) was compared by unadjusted log-rank test after approximately 65% of deaths. Effect of treatment on OS was examined across subgroups (including age, hormone receptor status and visceral disease). Pts alive or not known to have died were right-censored at last known date alive, including 20 pts in centers invited but who did not join the OS follow-up phase. Serious adverse events (SAEs) were recorded.
Results: 205 pts (median age 67.0 years) were randomized from 62 centers in 9 countries (fulvestrant 500 mg: n=102; anastrozole: n=103). The first pt enrolled on Feb 6, 2006. As of July 2014, 33/205 pts (16.1%) were known to be alive across both treatment groups and 137/205 (66.8%) pts had died. Median OS was significantly greater for fulvestrant 500 mg (54.1 months) vs anastrozole (48.4 months; HR 0.70; 95% CI 0.50, 0.98; p=0.041). OS analyses in pre-specified subgroups demonstrated a consistent treatment effect for fulvestrant 500 mg vs anastrozole (global interaction test p=0.755). The frequency of SAEs was similar between fulvestrant 500 mg (23.8%) and anastrozole (21.4%).
Conclusions: HR+ pts receiving first-line fulvestrant 500 mg lived significantly longer than pts on anastrozole (median OS difference of 5.7 months). A consistent OS treatment effect was observed across predefined subgroups. FIRST is therefore the second randomized trial to show an OS advantage for fulvestrant 500 mg over another endocrine therapy. No new safety signals were identified with longer-term treatment. Improved OS data provide further support for superior efficacy of fulvestrant 500 mg over anastrozole as first-line endocrine therapy for postmenopausal women with HR+ LA or MBC. If confirmation of superiority for fulvestrant 500 mg is seen in the Phase III FALCON study (NCT01602380), fulvestrant 500 mg should be considered for approval as a first-line agent in this setting.