7012 POSTER

Evaluation of the efficacy and safety of Tadalafil 20 mg on demand vs Tadalafil 5 mg once-a-day in the treatment of erectile dysfunction following curative radiotherapy for prostatic carcinoma: preliminary results of a randomized phase II trial

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Background: The purpose of the current study is to assess the efficacy and safety of once-a-day dosing of Tadalafil 5 mg versus Tadalafil 20 mg on demand, as a new treatment regimen for erectile dsysfunction (ED) following curative radiotherapy.
Materials and Methods: From January 2008 to April 2009, 35 eligible patients were randomized to 14 weeks of treatment with fixed doses of Tadalafil 20 mg on demand or Tadalafil 5 mg once-a-day in a 1:1 ratio. Primary efficacy measures included changes in the International Index of Erectile Function domain (IIEF), Sexual Encounter Profile (SEP) diary and tolerability. The global efficacy questions (GEQ) was added at the end of each treatment period. Side effects were categorized as absent, mild, moderate or severe.
Results: 30 patients completed the entire treatment protocol. The most common reasons for discontinuation were adverse events and patient's decision. Baseline characteristics were well balanced across the treatment groups. At 14 weeks, a significantly increase of IIEF domain score was observed in both arms. A comparison of mean scores of the IIEF questions before and after 4 and 12 weeks of treatment with Tadalafil 20 mg on demand or Tadalafil 5 mg once-a-day is reported in table 1.

Table 1: mean scores IIEF domains

	Tadalafil 20 mg on demand	Tadalafil 5 mg once-a-day
Baseline IIEF domain	5.7±3.1	6.7±4.7
After 1 month	24.7±7.1	25.8±4.4
After 3 months	26.3±7.1	27.4±1.1

Similarly, increased 4 and 12-weeks values of SEP (Tadalafil 5 mg, 74.1%; Tadalafil 20 mg, 75.7%) were observed in both groups. 84.6% of the patients in the Tadalafil 20 mg on demand arm responded positively to the GEQ about improvement of erections, while successful intercourse was reported in 100% of the patients in the Tadalafil 5 mg once-a-day arm. Mild adverse events occurred in a least 15% of patients and included dyspepsia, headache, back pain, upper abdominal pain and myalgia; only one patient discontinued because of severe adverse events.
Conclusions: Once-a-day Tadalafil 5 mg was well tolerated and significantly improved erectile function in men with erectile dysfunction after three-dimensional conformal radiotherapy or brachytherapy for prostatic carcinoma. Therefore, once-a-day dosing with Tadalafil 5 mg may be an attractive alternative to on demand therapy for ED.

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Phase II trial of the specific endothelin A receptor antagonist zibotentan (ZD4054) in pain-free or mildly symptomatic patients with hormone-resistant prostate cancer and bone metastases: final analysis of safety and efficacy

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Background: Here we report the final analysis of a Phase II trial of the specific ET_A-receptor antagonist zibotentan (ZD4054).
Methods: In this multicentre, parallel group, double-blind trial, pain-free or mildly symptomatic patients with HRPC and bone metastasis were randomized in a 1:1:1 ratio to receive once-daily zibotentan (10 or 15 mg/day po) or matching placebo. Time to progression (TTP) was the primary endpoint, and overall survival (OS) was a secondary endpoint. Study treatment discontinued on progression, which was a composite endpoint comprising clinical progression, requirement for opiate analgesia, worsening of or development of new soft tissue metastases, or death. The study was sized to detect a hazard ratio (HR) of 0.67 in TTP with 80% power at the 20% significance level. Data for progression and survival were analyzed using a Cox proportional hazards model.
Results: A total of 312 patients were randomized; all patients were included in the analyses. Baseline characteristics were similar between the groups. Median duration of treatment and follow-up were approximately 120 days and >600 days, respectively. Efficacy results are shown in the table. Improvements in overall survival were seen with zibotentan in both active treatment arms at all three analyses, but were less pronounced at the final analysis, which may reflect the prolonged follow-up beyond discontinuation of study treatment. Taxane usage after discontinuation from study treatment was similar across the three arms. The most common adverse events (AEs) were headache, peripheral oedema, and nasal congestion, each of which occurred in >30% of patients receiving zibotentan. Fewer than one third of patients experienced AEs of CTC grade 3 or above.

Median TTP and OS, months (HR vs placebo; 80% CI), and *P* vs placebo

	Placebo(n = 107)	Zibotentan 10 mg (n = 107)	Zibotentan 15 mg (n = 98)
Primary analysis			
TTP	3.6	4.0 (0.88; 0.71−1.09) P = 0.448	3.8 (0.83; 0.66−1.03) P = 0.278
OS	14.4	16.5 (0.38; 0.22−0.64) P = 0.019	15.1(0.61; 0.38−0.99) P = 0.190
Second analysis			
TTP	3.7	4.6 (1.09; 0.91−1.31) P = 0.553	3.8 (0.94; 0.78−1.14) P = 0.702
OS	17.3	24.5 (0.55; 0.41−0.73) P = 0.008	23.5 (0.65; 0.49−0.86) P = 0.052
Final analysis			
TTP	3.7	4.6 (1.06; 0.89−1.27) P = 0.673	3.8 (0.86; 0.72−1.04) P = 0.309
OS	19.9	23.5 (0.83; 0.67−1.02) P = 0.254	23.9 (0.76; 0.61−0.94) P = 0.103

Conclusion: Improvements in overall survival were seen with zibotentan in both active treatment arms. The OS benefit is being further investigated in the ENTHUSE Phase III clinical programme.
Trial sponsored by AstraZeneca (clinicaltrials.gov identifier NCT00090363).

7014 POSTER

A phase II study of sorafenib in combination with bicalutamide in patients with chemotherapy-naive Castrate Resistant Prostate Cancer (CRPC)

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Background: Sorafenib is a multi-targeted kinase inhibitor with activity against Raf and VEGFR. Sorafenib is associated with clinically discordant PSA changes in CRPC as a single agent, possibly due to effects on PSA production/secretion. Inhibition of the Ras-Raf-MAPK signaling pathway has been associated with restoration of androgen sensitivity in the androgen independent C4−2 cell line. The objective of this trial was to evaluate the clinical effects of sorafenib in combination with androgen receptor blockade in patients (pts) with chemotherapy-naive CRPC.
Material and Methods: Multicenter 2 stage design. Eligible pts had rising PSA >5, and minimal symptoms. Sorafenib 400 mg twice daily was administered with Bicalutamide 50 mg once daily on a 28-day cycle. Primary endpoint was PSA response ($\geqslant$50% decline confirmed) or stable disease $\geqslant$6 months. (P0 = 0.20, P1 = 0.4, α = 0.1, β = 0.1) Pts could continue therapy with rising PSA in the absence of other disease progression (objective disease or symptom progression).
Results: Study accrual is complete with 39 pts. Baseline characteristics: median age 75 (range 51−83), ECOG PS 0:1 in 25:14, median PSA = 46.8 (range 6.5−410). Metastatic sites nil:bone:lymph nodes:visceral in 8:24:18:2 pts. 33 pts had received at least one prior anti-androgen therapy. A median 5 cycles have been delivered (range 1−21) and 6 pts remain on protocal therapy. 17 (44%) pts have had either a PSA response or stable disease $\geqslant$6 months. Of 38 pts with PSA data available, PSA declines of $\geqslant$30% and $\geqslant$50% have occurred in 15 (39%) and 12(32%) pts respectively. 8 of 33 pts (24%) with prior anti-androgen use had a PSA response. Of the 15 pts with measurable disease, 9 (60%) had stable disease and 6 (40%) had progression as best response. Median time to treatment failure was 5.8 months (95% CI = 5.1−13.7) and median overall survival has not been reached (12 month survival = 82.2% (95% CI = 68.8−98.1%). Protocol therapy was discontinued in 11 pts due to adverse events (AE). Related grade 3/4/5 AE were fatigue (4 pts) and skin rash/hand-foot syndrome (17 pts). One pt died of presumed acute pancreatitis probably related to sorafenib.
Conclusions: The combination of bicalutamide and sorafenib was tolerable. PSA declines and prolonged stable disease were observed including in patients previously progressing on anti-androgens. Protocol defined criteria were met for further clinical investigation of this combination