First-in-human Phase I study of EZN-4176, a locked nucleic acid antisense oligonucleotide to exon 4 of the androgen receptor mRNA in patients with castration-resistant prostate cancer


BACKGROUND
Prostate cancer remains dependent of androgen receptor (AR) signalling, even after emergence of castration resistance. EZN-4176 is a third-generation antisense oligonucleotide that binds to the hinge region (exon 4) of AR mRNA resulting in full-length AR mRNA degradation and decreased AR protein expression. This Phase I study aimed to evaluate EZN-4176 in men with castration-resistant prostate cancer (CRPC).

METHODS
Patients with progressing CRPC were eligible; prior abiraterone and enzalutamide treatment were allowed. EZN-4176 was administered as a weekly (QW) 1-h intravenous infusion. The starting dose was 0.5 mg kg\(^{-1}\) with a 4-week dose-limiting toxicity (DLT) period and a 3+3 modified Fibonacci dose escalation design. After determination of the DLT for weekly administration, an every 2 weeks schedule was initiated.

RESULTS
A total of 22 patients were treated with EZN-4176. At 10 mg kg\(^{-1}\) QW, two DLTs were observed due to grade 3-4 ALT or AST elevation. No confirmed biochemical or soft tissue responses were observed. Of eight patients with <5 circulating tumour cells at baseline, a conversion to <5 was observed in three (38%) patients. The most common EZN-4176-related toxicities (all grades) were fatigue (59%), reversible abnormalities in liver function tests ALT (41%) and AST (41%) and infusion-related reactions including chills (36%) and pyrexia (14%).

CONCLUSION
Activity of EZN-4176 at the doses and schedules explored was minimal. The highest dose of 10 mg kg\(^{-1}\) QW was associated with significant but reversible transaminase elevation.