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PROSTATE CANCER

Antisense nucleic acids—tough delivery

First-in-human data of the locked antisense oligonucleotide (ASO) EZN-4176, which binds exon 4 of the androgen receptor (AR) mRNA (encoding the amino terminus), shows dosing to be limited by transaminase elevation with no evidence of target modulation at the highest tested doses. Whether amino-terminus targeting ASOs will advance clinically remains uncertain.

AR splice variants are thought to be central to AR-targeted therapy resistance in prostate cancer, but are not currently blocked by available therapies. Given that castration-resistant prostate cancer (CRPC) is characterized by AR signalling in spite of androgen depletion, using ASOs that bind to AR mRNA transcripts to promote their degradation holds promise for this condition. Indeed, preclinical data showed EZN-4176 could reduce AR expression *in vitro*.

Johann de Bono and colleagues enrolled 22 pretreated men with metastatic CRPC. Although the study was terminated before the maximum tolerated dose could be determined, no dose-limiting toxicity was observed at a weekly dose of 6.5 mg/kg. However, transaminase elevation was observed in several patients.

Interestingly, three of eight men with five or more circulating tumour cells (CTCs) at baseline, had fewer than five CTCs after 5 weeks of treatment. Two of these men had PSA declines of 18% and 26%, which suggests that EZN-4176, or other AR ASOs, might have clinical value.

Next-generation ASOs that can be delivered at concentrations that modulate AR expression without transaminase toxicity would be clinically useful. "More studies are needed that target the AR amino terminus, like EZN-4176, and these are currently being developed," commented de Bono.

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Original article Bianchini, D. *et al.* 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. *Br. J. Cancer* doi:10.1038/bjc.2013.619

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