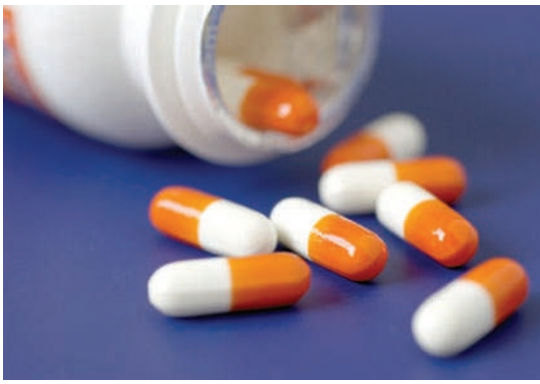
PROSTATE CANCER

MDV3100 has antitumor activity in castration-resistant disease



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Some castration-resistant prostate cancers remain dependent on androgen receptor signaling, even after testosterone levels are reduced to within the castrate range. Androgen receptor overexpression is thought to be responsible for this continued tumor growth, and has been shown to cause resistance to bicalutamide, currently the most widely used androgen receptor antagonist. MDV3100 is a novel androgen receptor antagonist with a number of unique features, including high receptor affinity, no agonist activity and the ability to induce tumor regression in bicalutamide-resistant models.

A phase I–II trial has demonstrated substantial antitumor activity for MDV3100 in patients with castration-resistant disease, including those who have previously received chemotherapy. "We evaluated patients who had progressed on not only one or multiple hormone therapies but also hormone therapies and chemotherapy," explains lead author Howard Scher. "We felt that simply making the decision to give chemotherapy would not change the biology of the cancer, and thus these tumors might also be hormonally sensitive."

MDV3100 was administered at doses of 30–600 mg per day to 140 men at five centers across the US, 75 of whom had been previously exposed to chemotherapy. The maximum tolerated dose was defined as 240 mg per day. Antitumor effects were demonstrated at all doses. Substantial reductions in serum PSA levels (>50%) were observed in a total of 78 men after 12 weeks of therapy. The proportion of patients with a maximum PSA decrease of >50% was no different between men who had received chemotherapy and those who had not (62% versus 51%; $P = 0.23$). Tumor response to MDV3100 was confirmed radiographically, with 22% of men demonstrating tumor regression. Furthermore, decreased glucose uptake was observed in 45% of the tumors assessed, and significant improvement in circulating tumor cell count was detected in 25 of 51 patients.

Notably, the investigators provided proof-of-concept for the action of MDV3100 in blocking androgen binding to tumors using PET. Reduced tumor tracer uptake (range 20–100%) was detected in all patients examined.

These results confirm the involvement of sustained androgen receptor signaling in castration-resistant prostate tumors and highlight the potential of MDV3100 as a treatment option. A phase III randomized trial of MDV3100 versus placebo, in men with castration-resistant prostate cancer who have previously received docetaxel, is currently underway.

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Original article Scher, H. I. *et al*. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1–2 study. *Lancet* **375**, 1437–1446 (2010)