ABSTRACT

Background: Androgen receptor (AR) antagonists have transformed prostate cancer patient care by targeting a key nodal point in tumor cell signaling. However, despite the impressive clinical activity of first- and second-generation antiandrogens, acquired resistance frequently emerges. Point mutations in the ligand-binding domain of AR, such as phenylalanine to leucine at position 877 (ARV877L), account for 10-20% of resistance. Such mutations are characterized by receptor activation, rather than inhibition, by first- and second-generation antiandrogen therapies.

JNJ-63576253 is a potent, high affinity competitive binder of wild type and mutant AR, including F877L. JNJ-63576253 blocks AR nuclear translocation, AR binding to DNA, and AR-dependent transcription. JNJ-63576253 inhibits the proliferation of androgen receptor driven prostate cancer cell lines, including those bearing ARV877L.

RESULTS

In the Herbie assay in male Sprague Dawley rats, oral administration of JNJ-63576253 was well tolerated and inhibited androgen sensitive organ (ASO) development in a dose-dependent manner. In male SHO mice bearing LNCaP xenografts with either wild type or ARV877L, daily treatment with 30 mg/kg JNJ-63576253 treatment resulted in statistically significant antitumor activity with no clinical side effects (i.e., photosensitivity, body weight loss), whereas second-generation antiandrogen enzalutamide had no antitumor efficacy in the LNCaP ARV877L mutant model.

Conclusions: Janssen and Tracor Pharma have entered a strategic licensing collaboration, whereby Tracor possesses exclusive rights for clinical development of JNJ-63576253 (now called TRC253). Tracor has entered TRC253 into PHA/2A clinical evaluation in metastatic castration-resistant prostate cancer patients.

OBJECTIVE

The aim of this study was to characterize the in vitro effects of JNJ-63576253 in AR expressing cells in competitive binding assays, reporter assays and for anti-proliferative activity in human prostate cancer cell lines; and investigate the AR antagonist activity of JNJ-63576253 using the Herbie assay in rats and probe its antitumor activity in paradigm LNCaP human prostate xenografts bearing either wild type or F877L mutant AR in mice.

RESULTS

JNJ-63576253 is potent, high affinity competitive binder of wild type AR and F877L mutant AR as shown in Table 1.

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INTRODUCTION

A. Schematic of therapeutics target of the AR Pathway. AR is bound to the nuclear chromoprotein HSP90 (HSP Complex) which prevents its degradation. HSP90 inhibitors cause AR degradation and decrease AR levels. In men treated with GnRH agonists to shut down testicular androgen synthesis, residual serum androgens are synthesized by the adrenal glands. In additional studies, evidence suggests intratumoral androgen synthesis.

B. In vitro and in vivo, the AR antagonist operates at the intercalary androgen receptor.

Abstract #1822

Antitumor Activity of JNJ-63576253 (TRC253), a Small Molecule Antagonist of F877L Mutant and Wild-Type Androgen Receptor


1Janssen & Discovery Oncology Tumor Biology, Spring House; 2Janssen & Discovery Oncology, Spring House; 3Janssen & Discovery Chemistry, Spring House; 4Janssen & R&D, Drug Metabolism and Pharmacokinetics Biocatalysis; 5Janssen & PDS-TLL, Spring House

Figure 1A. Androgen receptor pathway

Figure 1B. Androgen receptor F877L mutation

Figure 2: JNJ-63576253 demonstrates potent antagonistic activity against both wild type and F877L mutant AR.

Figure 3: JNJ-63576253 inhibits the androgen dependent proliferation of both wild type and F877L mutant AR driven tumors cells

Figure 4: JNJ-63576253 inhibits androgen sensitive organ (ASO) development in the Herbie assay

Figure 5: JNJ-63576253 inhibits tumor growth in human prostate cancer xenograft models, including F877L mutant AR