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MONOGRAPH

ORTERONEL

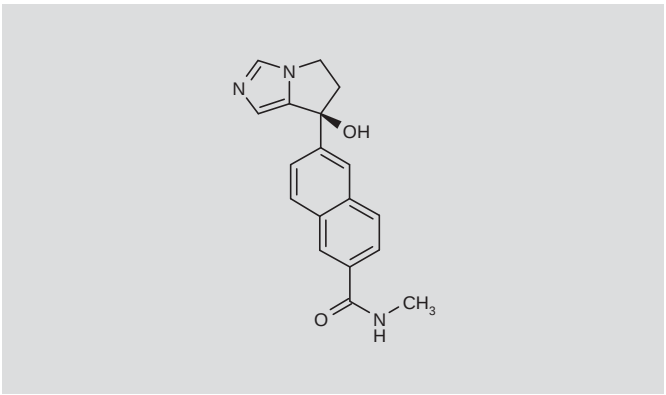
Prop INN; USAN

Androgen Biosynthesis Inhibitor
Steroid 17-alpha-Hydroxylase/17,20 Lyase Inhibitor
Oncolytic

TAK-700

6-[7(*S*)-Hydroxy-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-yl]-*N*-methylnaphthalene-2-carboxamide

InChI: 1S/C18H17N3O2/c1-19-17(22)14-3-2-13-9-15(5-4-12(13)8-14)18(23)6-7-21-11-20-10-16(18)21/h2-5,8-11,23H,6-7H2,1H3,(H,19,22)/t18-/m0/s1



$C_{18}H_{17}N_3O_2$

Mol wt: 307.3465

CAS: 566939-85-3

EN: 468971

SUMMARY

Prostate cancer is one of the most prevalent solid tumors in Western countries. Androgen ablation via surgical or chemical castration is an effective but transient therapy for advanced prostate cancer, particularly castration-resistant prostate cancer, a more aggressive disease for which there are limited treatment options. Orteronel (TAK-700), a novel, potent, selective, nonsteroidal oral inhibitor of the steroid 17-alpha-hydroxylase/17,20-lyase enzyme, is under development as a drug to inhibit androgen synthesis. Orteronel suppressed in vitro androgen production in human and monkey adrenal cells and in rat testicular cells, and administered orally to male monkeys it decreased the serum concentration of testosterone, dehydroepiandrosterone and, to a lesser extent, cortisol. In clinical trials in castration-resistant prostate cancer patients, orteronel decreased prostate-specific antigen, testosterone and dehydroepiandrosterone sulfate levels, and showed manageable toxicity. Ongoing phase II and III clinical trials will contribute to ascertain the safety and efficacy of orteronel in castration-resistant prostate cancer patients.

Key words: Castration-resistant prostate cancer – Androgen biosynthesis inhibitor – Orteronel – TAK-700

SYNTHESIS*

Orteronel can be prepared by several related strategies:

Chlorination of 6-bromo-2-naphthoic acid (I) with $SOCl_2$ (1, 2), optionally in the presence of DMF in THF (2), affords the corresponding acid chloride (II), which by reaction with $(i\text{-Pr})_2NH$ (1, 2), optionally in the presence of Et_3N in THF (2), provides amide (III). Metalation of 6-bromo-*N*,*N*-diisopropyl-2-naphthamide (III) with BuLi in THF followed by condensation with 1-tritylimidazole-4-carbaldehyde (IV) gives the diarylcarbinol (V), which by oxidation with MnO_2 in CH_2Cl_2 yields the corresponding ketone (VI) (1, 2). Compound (VI) can also be obtained directly by condensation of lithiated naphthamide (III) (by means of BuLi in THF) with *N*-methoxy-*N*-methyl-1-tritylimidazole-4-carboxamide (VII) (2). Asymmetric Reformatsky reaction of ketone (VI) with either bromo (2-ethoxy-2-oxoethyl)zinc (VIIIa) (1) or bromo (2-*tert*-butoxy-2-oxoethyl)zinc (VIIIb) (1, 2) [prepared in situ by reaction of *tert*-butyl bromoacetate (IX) with Zn and TMSCl (2)] by means of cinchonine, and optionally pyridine, in THF provides the 3(*S*)-hydroxy-3-(4-imidazolyl)-3-(2-naphthyl)propionic acid ethyl and *tert*-butyl esters (Xa) (1) and (Xb) (1, 2), respectively. Reduction of esters (Xa) or (Xb) by means of Red-Al in toluene yields the propane-1,3-diol derivative (XI), which by activation with MsCl in the presence of DIEA in THF followed by cyclization with MeOH in the presence of DIEA in acetonitrile affords the 7(*S*)-(2-naphthyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-ol derivative (XII). Finally, the *N*,*N*-diisopropylnaphthamide derivative (XII) is treated with CH_3NH_2 in the presence of BuLi in THF (1). Scheme 1.

Condensation of 1-tritylimidazole-4-carbaldehyde (IV) with ethyl acetate (XIII) using LDA in THF furnishes ethyl 3-hydroxy-3-(1-trityl-4-imidazolyl)propanoate (XIV), which by reduction with $LiAlH_4$ in THF affords diol (XV). Selective oxidation of the secondary alcohol of compound (XV) by means of MnO_2 in CH_2Cl_2 gives 3-hydroxy-1-(1-

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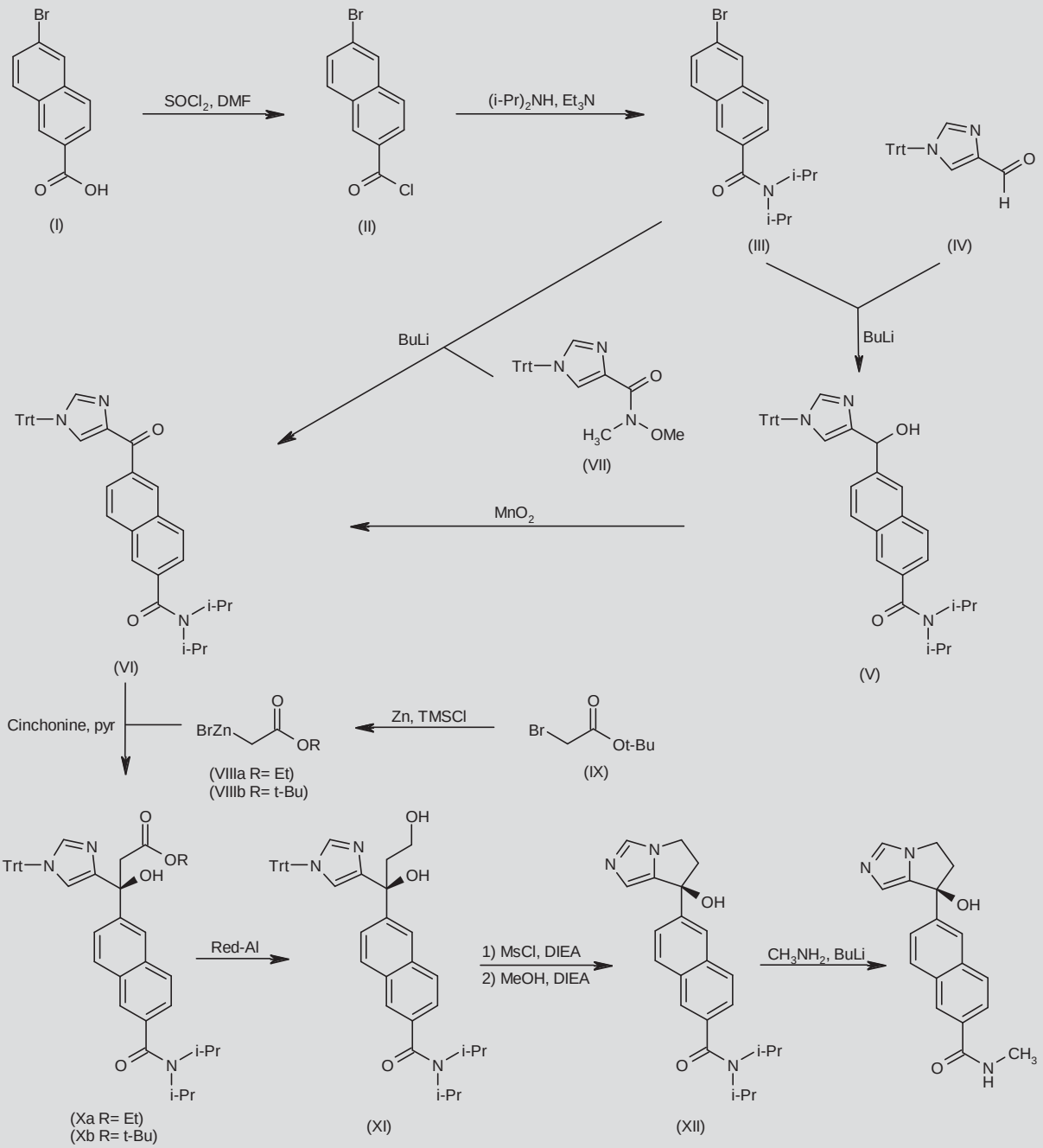
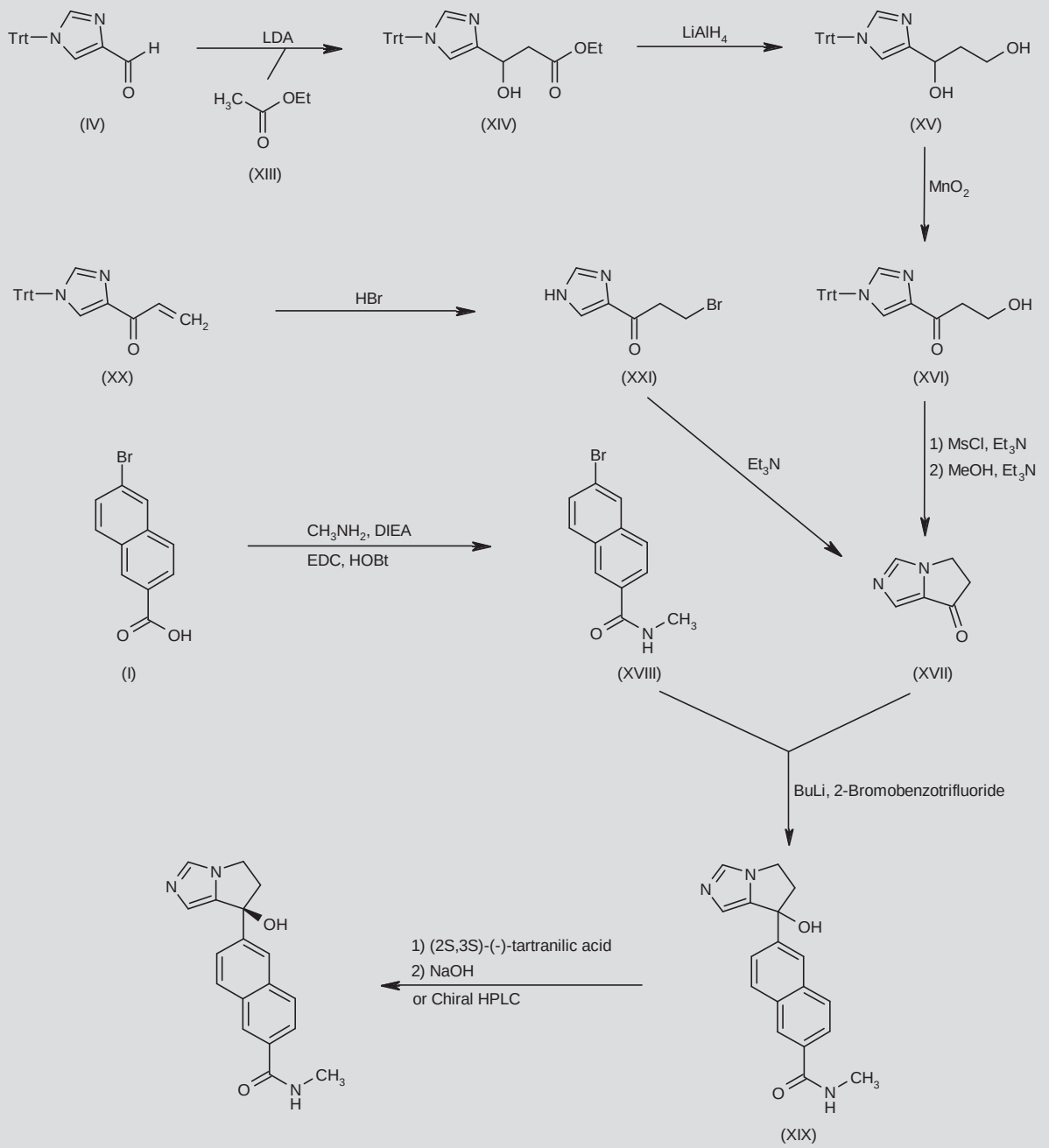
*Synthesis prepared by C. Estivill, J. Bolòs, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

Scheme 1. Synthesis of Orteronel



trityl-4-imidazolyl)-1-propanone (XVI), which upon hydroxyl group activation with MsCl and Et_3N in EtOAc followed by cyclization in the presence of Et_3N and MeOH in acetonitrile at 70 °C yields 5,6-dihydro-7*H*-pyrrolo[1,2-*c*]imidazol-7-one (XVII). Coupling of ketone (XVII) with metalated 6-bromo-*N*-methyl-2-naphthamide (XVIII) [prepared by amidation of 6-bromo-2-naphthoic acid (I) with CH_3NH_2 by means of EDC, HOBt and DIEA in DMF] with BuLi and optionally 2-bromobenzotrifluoride in THF provides the 7-(2-naphthyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-ol derivative (XIX), which is finally resolved by crystallization with (2*S*,3*S*)-(–)-tartranilic acid followed by addition of NaOH or by chiral HPLC separation (2, 3). Scheme 2.

Scheme 2. Synthesis of Orteronel



Intermediate (XVI) can alternatively be prepared by addition of HBr to 1-(1-trityl-4-imidazolyl)-2-propen-1-one (XX) in AcOH to afford the bromoketone (XXI) and then cyclization in the presence of Et_3N (2, 3). Scheme 2.

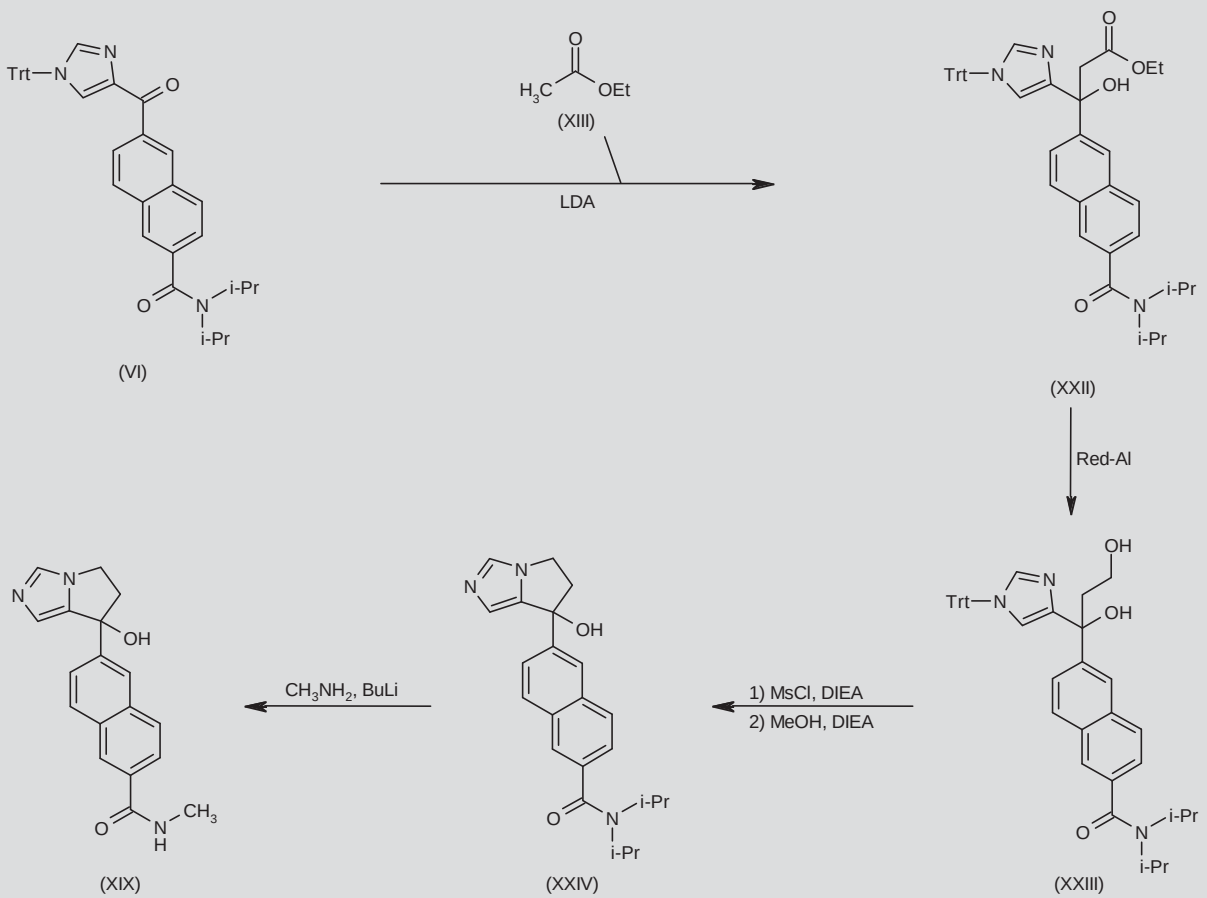
Alternatively, racemate (XIX) is obtained by aldol condensation of ketone (VI) with ethyl acetate (XIII) by means of LDA to yield the racemic β-hydroxy ester (XXII), which by reduction with Red-Al in toluene furnishes the corresponding diol (XXIII). Activation of diol (XXIII) with MsCl in the presence of DIEA in THF followed by cyclization by means of DIEA and MeOH in acetonitrile gives the 7-(2-naphthyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazol-7-ol derivative (XXIV). Finally, the *N*,*N*-diisopropyl-2-naphthamide derivative (XXVI) is treated with CH_3NH_2 in the presence of BuLi in THF (1-3). Scheme 3.

BACKGROUND

Prostate cancer is one of the most prevalent solid tumors in Western countries, the most common cancer in men and the second cause of death due to cancer in the U.S. (4). For instance, more than 58,000 men in Germany and more than 240,000 men in North America will be diagnosed with prostatic cancer in 2012 (4, 5). Organ-confined prostate cancer is curable by either radical prostatectomy or radiotherapy. In fact, low-risk tumors have a survival rate at 10 years of 90%, regardless of whether the tumors are treated or not (6). However, approximately 15% of prostate cancer patients have metastases at diagnosis, and a further 20% of patients will develop incurable metastases after failing local therapy (7).

Due to the hormonal dependency of the majority of prostate tumors (8), antiandrogenic hormone therapy has been the usual treatment for recurrent prostate cancer after radical prostatectomy and locally advanced or metastatic prostate cancers, when surgical treatment is not suitable. Antiandrogenic hormone therapy can be achieved by surgical castration (bilateral orchidectomy) or chemical castration (treatment with gonadotropin-releasing hormone analogues), but resistance to the therapy rapidly develops (9), and castration-resistant prostate cancer becomes a more aggressive disease, with a

Scheme 3. Synthesis of Intermediate (XIX)



median overall survival on the order of 16-18 months (10). This poor outcome and the lack of effective treatments have prompted the search for novel therapies, several of which are currently in clinical development for the treatment of castration-resistant prostate cancer, including androgen-modulating approaches, immunotherapies, angiogenesis inhibitors, serine/threonine-protein kinase mTOR pathway inhibitors, apoptosis-inducing drugs, insulin-like growth factor (IGF) pathway antagonists, epigenetic therapies and poly [ADP-ribose] polymerase (PARP) inhibitors (11).

Among the mechanisms involving the androgen receptor pathway that have been proposed to explain castration resistance (12), androgen receptor activation by androgens synthesized from adrenal androgens or by the de novo route intratumorally (13, 14) appears to be a feasible target for inhibition by a small molecule (15). The 17,20 lyase and steroid 17-alpha-hydroxylase activities of cytochrome P450 17A1 (steroid 17-alpha-hydroxylase/17,20 lyase; CYP17A1) play a pivotal role in the synthesis of androgens from cholesterol (16). In addition, the enzyme has been reported to be highly upregulated in castration-resistant prostate cancer metastases (14). Therefore, several small-molecule inhibitors of steroid 17-alpha-hydroxylase/17,20 lyase are currently under investigation as drugs to inhibit androgen synthesis (15).

Orteronel (TAK-700), a novel, potent, selective, nonsteroidal oral inhibitor of the enzyme, is currently in phase III clinical trials at Millennium Pharmaceuticals (The Takeda Oncology Company) for the treatment of metastatic castration-resistant prostate cancer (3, 17).

PRECLINICAL PHARMACOLOGY

In in vitro studies, orteronel inhibited human 17,20 lyase and 17-alpha-hydroxylase activities with IC_{50} values of 140 and 760 nM, respectively, while abiraterone –a selective, irreversible, steroidal inhibitor of CYP17A1 (18)– showed values of 27 and 30 nM, respectively. Consequently, orteronel has higher specificity for 17,20 lyase versus 17-alpha-hydroxylase than abiraterone (19-21). This specificity of orteronel may be relevant, because the 17-alpha-hydroxylase activity is necessary for the synthesis of cortisol, and decreased levels of cortisol stimulate the secretion of the adrenocorticotropic hormone, leading to hypertension via increased plasma levels of corticosterone and 11-deoxycorticosterone (15). In fact, hypertension is a common adverse effect of abiraterone (22).

Orteronel showed low inhibition of monkey 11-hydroxylase (IC_{50} > 10,000 nM), a key downstream enzyme that is proximal in corticosterone and cortisol biosynthesis, but not testosterone, thus suggesting that orteronel should have reduced effects on glucocorticoids at doses showing an antiandrogenic effect (20, 21).

In addition, orteronel inhibited human CYP17A1 with an IC_{50} of 19 nM, but showed IC_{50} values > 10 μM against human CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. In particular, for CYP3A4 the IC_{50} value was > 100 μM (1, 3, 19, 20). The specificity of orteronel for CYP17A1 over other CYP family enzymes, including other steroid synthesis enzymes and drug-metabolizing enzymes, suggests low toxicity and little drug–drug interactions (15).

Orteronel suppressed in vitro androgen production in human and monkey adrenal cells and in rat testicular cells. Indeed, in the human adrenocortical carcinoma cell line NCI-H295R, the production of dehydroepiandrosterone and androstenedione was inhibited by orteronel with IC_{50} values of 37 and 54 nM, respectively, while the production of cortisol was only moderately affected, with an IC_{50} value of 990 nM (19-21, 23, 24).

Orteronel administered orally as single or repeated doses (twice daily for 7 days) to intact male cynomolgus monkeys potently and dose-dependently decreased the serum concentration of testosterone, dehydroepiandrosterone and cortisol, although the latter to a lesser extent. Castrated male cynomolgus monkeys were also treated with orteronel in order to assess its effects on extragonadal sources of testosterone. In castrated monkeys, orteronel decreased serum concentrations of dehydroepiandrosterone and cortisol similar to in intact animals. Of note, in castrated monkeys orteronel further decreased the serum testosterone to a very low level (0.2-0.3 ng/mL), which was maintained during the treatment period, in contrast to intact monkeys where the suppression of testosterone was attenuated from the second day of treatment, probably due to activation of the hypothalamus–pituitary–gonadal axis (1, 3, 19-21, 23).

The effects of orteronel on androgen synthesis in rats were studied in vivo. Single oral doses of orteronel (100 and 300 mg/kg) significantly decreased the serum levels of testosterone in intact male rats. Multiple doses of orteronel (37.5, 150 or 600 mg/kg three times daily for 4 days) reduced the weight of prostate and seminal vesicles in male rats. These results were consistent with in vitro studies in rat testicular cells, where orteronel suppressed the production of testosterone and androstenedione (24).

PHARMACOKINETICS AND METABOLISM

Pharmacokinetic studies of orteronel in monkeys showed a good oral bioavailability (71%), with a t_{max} of 1.7 hours and a $t_{1/2}$ of 3.8 hours (1, 19, 21).

The pharmacokinetics of orteronel were studied in castration-resistant metastatic prostate cancer patients in an open-label phase I/II trial. Orteronel administered orally in the range of 100-600 mg twice daily showed dose-proportional exposure in phase I of the study, and from the efficacy and safety data the recommended dose for phase II of the study was 400 mg b.i.d. (25, 26).

SAFETY

In vitro, orteronel showed no significant effects in enzyme and radioligand binding assays. In a 4-week toxicity study in monkeys, orterenol administered orally at 0.8, 4, 20 and 100 mg/kg/day showed several changes, most related to the pharmacology of the compound, including a decrease in plasma cortisol levels, an increase in the weight of adrenal glands and a decrease in testes and prostate weights at the highest dose. These changes were almost completely reverted at the end of the 4-week recovery period (20).

The safety of orteronel administered orally in the range of 100-600 mg twice daily was studied in castration-resistant metastatic prostate cancer patients in the open-label phase I/II trial (25-27). At 12 weeks of treatment, 50% of patients had discontinued (including 13% due to adverse events and 16% to disease progression). The most common adverse events were fatigue (72%), nausea (44%) and

constipation (31%). The most common grade 3 or greater adverse events were fatigue and diarrhea. Orteronel at doses of 300 mg b.i.d. or higher appears to be well tolerated (27).

The safety of orteronel (300 mg b.i.d.) was assessed in 38 patients with non-metastatic castration-resistant prostate cancer and rising prostate-specific antigen levels in a phase II trial. Eight men discontinued orteronel due to adverse events. The most common grade 3 or greater adverse events were dyspnea, hypertension, fatigue, hypokalemia and pneumonitis (28).

The safety of orteronel (400 mg b.i.d.) plus prednisone (5 mg b.i.d.) is currently being assessed in patients with chemotherapy-naive metastatic castration-resistant prostate cancer in an ongoing phase III trial (29).

CLINICAL STUDIES

The efficacy of orteronel was assessed in an open-label, dose-escalation phase I/II trial in castration-resistant metastatic prostate cancer patients (25-27). Orterenol was administered orally at doses ranging from 100 to 600 mg b.i.d., and at 400 mg b.i.d. combined with prednisone 5 mg b.i.d. At 4 weeks in the phase I portion of the study, all patients treated with orteronel at the dose of 300 mg or higher showed a prostate-specific antigen decrease of 50% or more in 80% of patients and of 90% or more in 27% of patients. All patients treated with orteronel showed decreases in median testosterone (from 5.5 to 0.6 ng/dL) and dehydroepiandrosterone sulfate (from 50.0 µg/dL to below limit of quantification) levels (26). In the phase II portion of this study four additional doses were included, and circulating tumor cells were determined. At 12 weeks patients showing a prostate-specific antigen decrease of 50% or more, reaching 63%, 52%, 41% and 62%, respectively, in the groups receiving 300 mg b.i.d., 400 and 600 mg b.i.d. plus prednisone, and 600 mg once daily. All treatment groups showed decreases in median testosterone and dehydroepiandrosterone sulfate levels, and in mean circulating tumor cells. Of note, around half of the patients with circulating tumor cells of 5 cells per 7.5 mL at baseline converted to less than 5 cells per 7.5 mL, and this shift may represent a better predictor of overall survival than changes in prostate-specific antigen levels (30). Therefore, orteronel at doses of 300 mg or more appears to be active in patients with metastatic castration-resistant prostate cancer, with similar efficacy whether prednisone was added or not (27, 30).

The efficacy of orteronel was assessed in patients with nonmetastatic castration-resistant prostate cancer and rising prostate-specific antigen in a phase II trial. Orteronel was administered orally at 300 mg b.i.d. to 38 patients with a median age of 71 years. After 3 months of treatment, 11% of patients achieved prostate-specific antigen levels of 0.2 ng/mL or less, which was the primary endpoint for efficacy. At 3 and 6 months of treatment, the percentage decline in mean prostate-specific antigen levels was 83% and 87%, respectively, and in testosterone levels 89% and 86%, respectively (28).

The efficacy of orteronel (400 mg b.i.d.) plus prednisone (5 mg b.i.d.) is currently being studied in chemotherapy-naive metastatic castration-resistant prostate cancer patients in an ongoing phase III trial (NCT01193244). A parallel phase III study is gauging the same treatments in patients who have received docetaxel-based therapy for metastatic castration-resistant prostate cancer (NCT01193257) (29). These two phase III trials are both recruiting patients, and the estimated primary completion dates are January and September 2013, respectively, according to ClinicalTrial.gov (17).

CONCLUSIONS

Castration-resistant prostate cancer is an aggressive disease with a median overall survival on the order of 16-18 months. This poor outcome and the lack of effective treatments have prompted the search for novel therapies that are currently in clinical development.

Orteronel, a novel, selective, potent, nonsteroidal oral inhibitor of the 17,20 lyase enzyme, is under development as a drug to inhibit androgen synthesis. Orteronel suppressed in vitro androgen production in human and monkey adrenal cells and in rat testicular cells. Orteronel administered orally to intact or castrated male cynomolgus monkeys decreased the serum concentration of testosterone, dehydroepiandrosterone and, to a lesser extent, cortisol. Notably, in castrated monkeys orteronel further decreased serum testosterone to a very low level, which was maintained during the treatment period. In clinical trials in castration-resistant prostate cancer patients, orteronel decreased prostate-specific antigen, testosterone and dehydroepiandrosterone sulfate levels, and demonstrated manageable toxicities.

Phase II and III clinical trials are ongoing devoted to assessing the safety and efficacy of orteronel in the treatment of metastatic castration-resistant prostate cancer.

SOURCES

Millennium Pharmaceuticals, Inc. (US); Takeda Pharmaceuticals Co., Inc. (JP).

DISCLOSURES

The author states no conflicts of interest.

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