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## Orteronel for the treatment of prostate cancer

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### Abstract

Orteronel (also known as TAK-700) is a novel hormonal therapy that is currently in testing for the treatment of prostate cancer. Orteronel inhibits the 17,20 lyase activity of the enzyme CYP17A1, which is important for androgen synthesis in the testes, adrenal glands and prostate cancer cells. Preclinical studies demonstrate that orteronel treatment suppresses androgen levels and causes shrinkage of androgen-dependent organs, such as the prostate gland. Early reports of clinical studies demonstrate that orteronel treatment leads to reduced prostate-specific antigen levels, a marker of prostate cancer tumor burden, and more complete suppression of androgen synthesis than conventional androgen deprivation therapies that act in the testes alone. Treatment with single-agent orteronel has been well tolerated with fatigue as the most common adverse event, while febrile neutropenia was the dose-limiting toxicity in a combination study of orteronel with docetaxel. Recently, the ELM-PC5 Phase III clinical trial in patients with advanced-stage prostate cancer who had received prior docetaxel was unblinded as the overall survival primary end point was not achieved. However, additional Phase III orteronel trials are ongoing in men with earlier stages of prostate cancer.

### Keywords

17, 20 lyase; CYP17A1; orteronel; prostate cancer; TAK-700

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Prostate cancer is the most common cancer among men in the USA, with over 220,000 new cases of prostate cancer predicted for 2013 [1]. Prostate cancer is also the second most lethal cancer in the USA, and over 28,000 men are predicted to die of this disease this year [1].

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#### Information resources

Yamaoka *et al.* describes the effects of orteronel treatment both *in vitro* and *in vivo* in preclinical studies [14].

Nearly all prostate cancer deaths are due to metastatic tumors that have progressed despite androgen deprivation therapies (ADTs) that work principally by suppressing androgen synthesis in the testes. The target of ADT is the androgen receptor (AR), a nuclear hormone receptor activated by androgen ligands. The AR is critical for both proliferation and the differentiation state of prostate cancer cells.

ADT with luteinizing hormone-releasing hormone (LHRH) agonists or LHRH antagonists is the first-line treatment for metastatic prostate cancer. While most patients initially respond to ADT, tumor progression termed 'castration resistance' is universal. This castration-resistant state is defined by a continued rise in prostate-specific antigen (PSA) or progression of metastases in the setting of castrate serum levels of testosterone (<50 ng/dl). However, despite the fact that serum levels of testosterone are reduced with ADT, androgens persist within tumors from men with castration-resistant prostate cancer (CRPC) [2]. In addition, androgen synthetic enzymes are frequently upregulated in CRPC tumors, and AR overexpression and AR mutations are also common, demonstrating the continued importance of AR signaling [2–4].

These results led to the development of newer, more potent forms of ADT. These drugs include the CYP17A inhibitor abiraterone acetate and the novel AR antagonist enzalutamide. Treatment with both agents interferes with persistent intratumoral androgens and suppresses CRPC cell growth in preclinical studies [5,6]. Furthermore, treatment with abiraterone acetate or enzalutamide in Phase III clinical trials in men with metastatic CRPC leads to clinical benefit, including significant prolongation of both progression-free and overall survival with the exception of the abiraterone Phase III clinical trial in men with metastatic CRPC who had not received prior docetaxel chemotherapy [7–9]. That trial only showed a significant improvement in progression-free survival [8]. While abiraterone acetate and enzalutamide are effective in many CRPC patients, these treatments are noncurative. Thus, novel therapies are required to provide more durable tumor control in patients with CRPC.

## Overview of the market

Abiraterone acetate was the first novel hormonal therapy approved for the treatment of metastatic CRPC in the past 2 years. Abiraterone acetate inhibits CYP17A1 (both the 17 $\alpha$ -hydroxylase and 17,20 lyase activities of this enzyme) in the steroid biosynthesis pathway. Suppression of 17 $\alpha$ -hydroxylase leads to reduced cortisol synthesis and compensatory overproduction of mineralocorticoids. Therefore, prednisone is administered concomitantly with abiraterone acetate to suppress the adrenocorticotrophic hormone overdrive that results in hypertension, hypokalemia and edema and to prevent adrenal insufficiency. Currently, abiraterone acetate is approved for metastatic CRPC patients both prior to and after treatment with docetaxel chemotherapy based on the results of two recent Phase III clinical trials [7,8]. Enzalutamide is a novel AR antagonist that prevents androgens from binding to and activating the AR. Treatment with enzalutamide in a Phase III clinical trial in patients who had received prior docetaxel demonstrated improved overall survival and progression-free survival [9]. A Phase III enzalutamide clinical trial in patients with metastatic CRPC who had not yet received docetaxel chemotherapy was recently unblinded after interim

analysis showed a significant improvement in overall survival and progression-free survival. Sipuleucel-T [10], a form of immunotherapy, docetaxel chemotherapy [11], cabazitaxel chemotherapy [12], and the  $\alpha$ -emitting radiopharmaceutical radium-223 [13] have all demonstrated improved overall survival in Phase III clinical trials with men with CRPC. These drugs are the other approved treatment options for men with metastatic CRPC.

## Introduction to the compound

Orteronel is a novel, nonsteroidal inhibitor androgen synthesis with greater specificity for 17,20 lyase versus 17 $\alpha$ -hydroxylase. Orteronel is manufactured by Millennium: The Takeda Oncology Company (MA, USA) (Figure 1).

## Chemistry

Like abiraterone acetate, orteronel is an inhibitor of the steroidogenic enzyme CYP17A1. However, orteronel has higher specificity for the 17,20 lyase activity of CYP17A1, while abiraterone acetate potently inhibits both CYP17A1's 17,20 lyase and 17 $\alpha$ -hydroxylase activities [14]. The increased specificity of orteronel inhibition potentially means less disruption to the glucocorticoid biosynthesis pathway (Figure 2) and less inhibition of other CYP enzymes, many of which are important for drug metabolism. Despite this, many of the orteronel clinical trials have included prednisone coadministration. Possible explanations for this are that the placebo arm of these trials included prednisone or owing to the concern of the risk of adrenal insufficiency with prolonged orteronel treatment.

Structurally, the fused imidazole ring system within orteronel makes it an attractive ligand for the catalytic heme iron that is found in many CYP enzymes. Orteronel's selectivity for CYP17A1's 17,20 lyase activity over 17 $\alpha$ -hydroxylase and other CYP enzymes, such as CYP3A, is attributed to its conformational rigidity and low ClogP index (a measure of lipophilicity) [15].

## Preclinical studies

**Pharmacokinetic characteristics**—Preclinical studies demonstrate that orteronel has high bioavailability and a favorable area under the curve profile with oral administration [14,16]. Orteronel levels in the testes and adrenal glands in rats treated with orteronel peaked at 6 h with similar clearance kinetics across all tissue types tested [16]. Examination of orteronel's molecular structure along with clearance kinetics suggest that CYP17A1 inhibition with orteronel is reversible, unlike abiraterone acetate [15,16].

**Pharmacodynamics**—Orteronel was 5.4-times more potent for inhibition of human 17,20 lyase activity versus 17 $\alpha$ -hydroxylase activity in a cell-free enzyme assay [14]. These results were further validated in culture using human adrenal tumor cells treated with varying concentrations of orteronel or abiraterone acetate and monitored for the downstream 17,20 lyase metabolite dehydroepiandrosterone (DHEA) and the 17 $\alpha$ -hydroxylase metabolite cortisol. Orteronel treatment led to potent suppression of DHEA – 27-fold more than cortisol suppression. Conversely, in the same assay, abiraterone acetate led to more similar suppression of DHEA and cortisol, highlighting orteronel's specificity for 17,20

lyase inhibition. Similarly, in another study when rat testicular cells were treated with orteronel in culture, testosterone was potently inhibited with little effect on corticosterone [16].

In experiments with uncastrated rats, orteronel treatment significantly suppressed serum testosterone levels and decreased the overall weight of several androgen-dependent organs [16]. Furthermore, twice daily (b.i.d.) administration of orteronel in cynomolgus monkeys significantly reduced serum DHEA and testosterone levels compared with vehicle treatment [14,15]. Importantly, when orteronel treatment was combined with castration in these animals, testosterone levels were further suppressed versus castration alone, and this suppression was sustained throughout the duration of treatment. These results provided the rationale to test orteronel in patients with advanced prostate cancer.

## Clinical studies

**Phase I trials with orteronel in metastatic CRPC**—The results of a Phase I/II dose-escalation study in 26 patients with metastatic CRPC were presented at the 2010 American Society of Clinical Oncology annual meeting [17]. That study evaluated b.i.d. orteronel at five dose levels: 100, 200, 300, 400 and 600 mg. An additional six patients received orteronel 400 mg b.i.d. plus prednisone 5 mg b.i.d. Six patients discontinued therapy due to adverse events (AEs), four owing to radiographic progression, two owing to PSA progression, two owing to patient request and one for ‘other reasons’. In total, 92% of patients experienced a drug-related AE, including 54% with grade 3 AEs. The most common treatment-emergent AEs were fatigue (65%), nausea (42%), constipation (38%), anorexia (35%) and vomiting (27%). At 4 weeks, testosterone levels decreased from 5.5 ng/dl to a median level of 0.6 ng/dl and DHEA decreased from 50.0 µg/dl to ‘unquantifiable levels’ in all patients. Of the cohorts that received 300 mg of orteronel for three cycles and had PSA levels measured at 3 months, 80% of patients had a 50% PSA decline and 27% had a 90% PSA decline (Tables 1 & 2).

Petrylak *et al.* presented a Phase I study of docetaxel in combination with orteronel at the 2012 American Society of Clinical Oncology annual meeting [18]. In this study, orteronel was given b.i.d. with prednisone (5 mg b.i.d.) starting on day 8 of cycle one. A 3 + 3 dose escalation was used with a starting orteronel dose of 200 mg b.i.d. The dose was increased to 400 mg b.i.d.; a total of 14 men with metastatic CRPC were treated in this study. The only dose-limiting toxicity was grade 3 febrile neutropenia. A total of 11 men, including both dose groups, had a treatment-related grade 3 AE, including neutropenia (50%), hyperglycemia (21%), febrile neutropenia (14%), infusion reaction (14%) and hyponatremia (14%). The 400-mg dose also had the unique AE of hypophosphatemia. Five of 14 men had serious drug-related AEs. The most common serious drug-related AE was febrile neutropenia in two patients. At 3 months, 86% of patients had a 50% PSA decline, while 36% had a 90% PSA decline. Median testosterone levels declined to 0.2 ng/dl. The addition of orteronel to docetaxel appeared to have no evidence of AE potentiation, and orteronel 400 mg b.i.d. was the chosen dose for the subsequent Phase II study.

**Phase II studies with orteronel in metastatic CRPC**—Petrylak *et al.* subsequently performed the Phase II study using orteronel 400 mg b.i.d. plus docetaxel/prednisone [19]. The primary end points were: safety, pharmacokinetics and PSA response. Secondary objectives included: time to PSA progression and/or radiographic progression and radiographic response using Response Evaluation Criteria In Solid Tumors 1.1. At the time of that report, 24 men had been treated, and 12 remained on study. Nine men discontinued treatment due to AEs. All men experienced at least one grade 3 AE, and 23 were reported to be treatment-related. The most common treatment-related grade 3 AEs were neutropenia (38%), fatigue (21%), leukopenia (13%), and dehydration (13%). Two patients died in the study from causes that were felt to be unrelated to the treatment (disease progression and respiratory failure). At 3 months, 18 men were evaluable for PSA response. In total, 72% of men experienced a 50% PSA decline and 28% experienced a 90% PSA decline. Median testosterone levels decreased from 6.8 to 0.2ng/dl at 3 months. The overall objective response rate was 56%. Median time to PSA progression was 6.1 months, and median time to radiographic progression was not reached. There was no evidence of drug–drug interactions between orteronel and docetaxel/prednisone.

Agus *et al.* presented results from a Phase I/II study at the 2012 Genitourinary American Society of Clinical Oncology annual meeting. That trial evaluated four orteronel dose cohorts (300 mg b.i.d., 400 mg b.i.d. plus prednisone 4 mg b.i.d., 600 mg b.i.d. plus prednisone 4 mg b.i.d. and 600 mg daily [q.d.]) in 97 subjects with metastatic CRPC who had no prior chemotherapy exposure [20]. A total of 19% of subjects were withdrawn from the study owing to AEs. The most common AEs were fatigue (76%), nausea (47%) and constipation (38%). The most common grade 3 AEs were fatigue (12%) and hypokalemia (8%). PSA response rates (50% PSA decline) at 12 weeks were 63, 50, 41 and 60% in the 300 mg b.i.d., 400 mg b.i.d. plus prednisone, 600 mg b.i.d. plus prednisone and 600 mg q.d. groups, respectively. Testosterone and DHEA levels decreased on study in all dose cohorts, and mean circulating tumor cell levels decreased from 16.6 per 7.5 ml of blood to 3.9 at 12 weeks.

**Phase II studies with orteronel in nonmetastatic CRPC**—Two abstracts presented data from a Phase II study evaluating the efficacy of orteronel 300 mg b.i.d. without concomitant steroids in 38 men with nonmetastatic CRPC [21,22]. The primary end point was the percentage of men who achieved a PSA 0.2 ng/ml at 3 months. Secondary end points included: safety, PSA kinetics, progression-free survival, time to PSA progression, time to metastases, changes in endocrine and bone markers, changes in bone mineral density and circulating tumor cell counts. The median duration of therapy was 12.4 months. A total of 12 patients discontinued the study owing to AEs, including two cases of possible adrenal insufficiency. The most common grade 3 AE was hypertension in seven patients [22]. In total, 14 patients experienced other grade 3 AEs, including dyspnea (8%), fatigue (5%), hypokalemia (5%) and pneumonitis (5%) [21]. At 3 months, median testosterone declined by 89% to 0.78 ng/dl, median adrenocorticotrophic hormone increased by 171%, and median cortisol declined by 21% but remained within normal range. A total of 18% of patients had a PSA 0.2 ng/ml at 3 months [21,22] with 76 and 32% of men achieving a 50% PSA decline or 90% PSA decline, respectively [21]. At 6 months, 45% of men experienced a

50% PSA decline, and 21% of men experienced a 90% PSA decline [21]. The median time to PSA progression and progression-free survival were both 13.8 months. The 1-year metastasis-free survival was 94%, and the 2-year metastasis-free survival was 69% [22].

**Phase III orteronel studies**—There are currently five ongoing Phase III studies evaluating the role of orteronel in various stages of prostate cancer.

**Phase III studies with orteronel in metastatic CRPC after docetaxel chemotherapy**

ELM-PC 5 was a Phase III multicenter, randomized, double-blind, placebo-controlled study evaluating orteronel 400 mg b.i.d. plus prednisone 5 mg b.i.d. versus placebo plus prednisone (randomized 2:1) in 1099 men with metastatic CRPC who had radiographic evidence of progression within 6 months of receiving a cumulative dose of 225 mg/m<sup>2</sup> of docetaxel. The primary end point was overall survival. Secondary end points included: radiographic progression-free survival, PSA response rate, pain response, safety, time to PSA progression, circulating tumor cell and endocrine marker levels, and patient-reported outcomes. At the prespecified interim analysis, orteronel plus prednisone compared with the control arm was unblinded after orteronel failed to meet the primary end point of improved overall survival. The median overall survival was 17.0 months (95% CI: 15.2–19.9) in the orteronel arm versus 15.2 months (95% CI: 13.5–16.9) in the placebo arm (HR: 0.886 [95% CI: 0.739–1.062]; p = 0.1898) [23]. However, radiographic progression-free survival was significantly improved with a median of 8.3 months for orteronel treatment versus 5.7 months with placebo (HR: 0.76 [95% CI: 0.653–0.885]; p = 0.00038) [23]. On 25 July 2013, Takeda Pharmaceutical Company Limited (Osaka, Japan) made the decision to unblind the study and allow patients to continue taking orteronel at the discretion of their treating physicians. It will be important to determine the proportion of patients in each arm who went on to receive other life-extending therapies after withdrawal from the study. Subsequent treatment of patients from the placebo arm with drugs, such as abiraterone acetate or enzalutamide, may explain why this study demonstrated an improvement in progression-free survival without an improvement in overall survival.

SAKK 08/11 is a Phase III Swiss multicenter, randomized, double-blind, placebo-controlled study designed to determine the role of maintenance orteronel. A total of 192 men with metastatic CRPC who have stable disease (based on PSA and imaging) after receiving a cumulative dose of 300 mg/m<sup>2</sup> of docetaxel will be enrolled on this trial. Orteronel 300 mg b.i.d. plus best supportive care will be compared with placebo plus best supportive care. The primary end point is event-free survival. Secondary end points include: safety, PSA response, time to PSA progression, radiographic progression-free survival, quality of life, pain response and overall survival.

**Phase III studies with orteronel in metastatic CRPC prior to docetaxel**

ELM-PC 4 is a Phase III study evaluating orteronel 400 mg b.i.d. plus prednisone 5 mg b.i.d. versus placebo plus prednisone in chemotherapy-naive patients [24]. Planned enrollment is 1454 patients. Patients who require opiates for bone pain or who have received ‘adrenal-targeting therapy’ or chemotherapy in the past 2 years are excluded. The primary end points include: radiographic progression-free survival and overall survival. Secondary end points include: PSA response rate ( 50% decline) at 12 weeks, time to pain

progression and change in circulating tumor cell numbers. Two interim analyses are planned, but results have yet to be released.

#### **Phase III study with orteronel in metastatic ADT-naive prostate cancer—**

SWOG-1216 is an on-going Phase III multicenter, randomized, controlled study evaluating orteronel versus the AR antagonist bicalutamide as part of a combined androgen blockade with an LHRH agonist in men with newly diagnosed, ADT-naive metastatic prostate cancer. A total of 1486 men will be randomized to LHRH agonist plus orteronel 300 mg b.i.d. versus LHRH agonist plus bicalutamide 50 mg q.d. Patients must not have received chemotherapy, abiraterone acetate, ketoconazole or enzalutamide for metastatic disease, but are allowed to have received neoadjuvant or adjuvant chemotherapy for curative intent if these were given 2 years prior to enrollment. The primary end point is overall survival.

#### **Phase III study with orteronel in high-risk localized prostate cancer—**

RTOG-1115 is a Phase III multicenter, randomized, controlled study evaluating radiation therapy plus combined androgen blockade (LHRH agonist plus an AR antagonist) with or without the addition of 2 years of orteronel treatment b.i.d. The sample size is 900, and this trial focuses on men with high-risk localized prostate cancer. The primary end point is overall survival. Secondary end points include: safety, prevention of biochemical (PSA) recurrence, progression-free survival, prostate cancer-specific survival, quality of life measures, testosterone levels and clinical survivorship end points.

### **Safety & tolerability**

Overall, orteronel appears to be well tolerated in doses ranging from 200 to 600 mg b.i.d. (Table 2). In Phase I clinical studies, the only dose-limiting toxicity was grade 3 febrile neutropenia with orteronel 400 mg b.i.d. in combination with docetaxel chemotherapy [18]. In Phase II studies, the most common AEs were fatigue, nausea and constipation [18,20]. Grade 3 AEs included neutropenia (with orteronel in combination with docetaxel), fatigue, hypokalemia, dyspnea, pneumonitis and hypertension [17–18,20–21]. Two out of 38 men treated with orteronel without steroids developed adrenal insufficiency [21,22]. The addition of orteronel to docetaxel/prednisone reportedly had no evidence of AE potentiation or drug–drug interactions [18,19].

In the ELM-PC 5 Phase III study of orteronel plus prednisone versus placebo plus prednisone, the most common drug-related AEs (any grade) included: nausea (30% orteronel, 16% placebo), vomiting (23% orteronel, 8% placebo) and fatigue (17% orteronel, 11% placebo) [23]. The most common grade 3 drug-related AEs included: elevated lipase (12% orteronel, <1% placebo), increased amylase (8% orteronel, <1% placebo) and fatigue (3% orteronel, 3% placebo) [23].

Ongoing Phase III studies are currently evaluating orteronel 300 or 400 mg b.i.d. doses. We await the safety results with these doses in these larger trials.

## Conclusion

Orteronel is a novel CYP17A1 inhibitor that effectively suppresses androgen synthesis and PSA values in single agent Phase I and II studies [17,20–22], and in studies in combination with docetaxel chemotherapy [18,19]. As orteronel has greater effects on 17,20-lyase versus 17- $\alpha$ -hydroxylase, it may be possible to avoid concomitant corticosteroid administration. Indeed, orteronel regimens without steroids have been safely administered with only rare cases of adrenal insufficiency [21,22]. Overall, orteronel is well tolerated with the most common reported AEs of: fatigue, neutropenia, hypokalemia, nausea, vomiting, constipation, hypertension, dyspnea and pneumonitis [17–22]. An interim analysis of a Phase III clinical trial with orteronel in patients with metastatic CRPC who had received prior docetaxel chemotherapy did not achieve its primary end point of overall survival [23]. This is in contrast to Phase III trials of other novel hormonal agents, abiraterone acetate and enzalutamide, that did demonstrate improved overall survival in a similar patient group [7,9]. Additional Phase III studies are currently underway to determine if orteronel improves survival for CRPC patients in the prechemotherapy setting, where abiraterone acetate is already approved and where it is likely that enzalutamide will soon be approved based on a recent analysis of the PREVAIL trial. We await the results of this orteronel trial and trials of orteronel in even earlier disease states to determine whether orteronel will be added to an expanded arsenal of treatments to combat advanced prostate cancer.

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## EXECUTIVE SUMMARY

### Mechanism of action

- Orteronel is a novel, oral, nonsteroidal, selective inhibitor of CYP17A1 that suppresses androgen production.

### Pharmacokinetic/pharmacodynamic properties

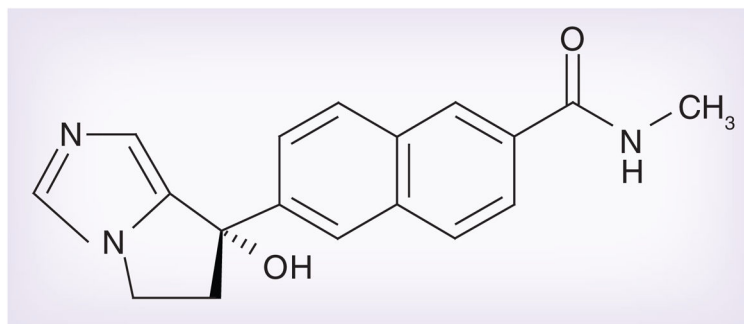
- Orteronel has high bioavailability as both an oral and intravenous agent.
- Orteronel is a more potent inhibitor of CYP17A1's 17,20 lyase activity compared with its 17 $\alpha$ -hydroxylase activity.

### Clinical efficacy

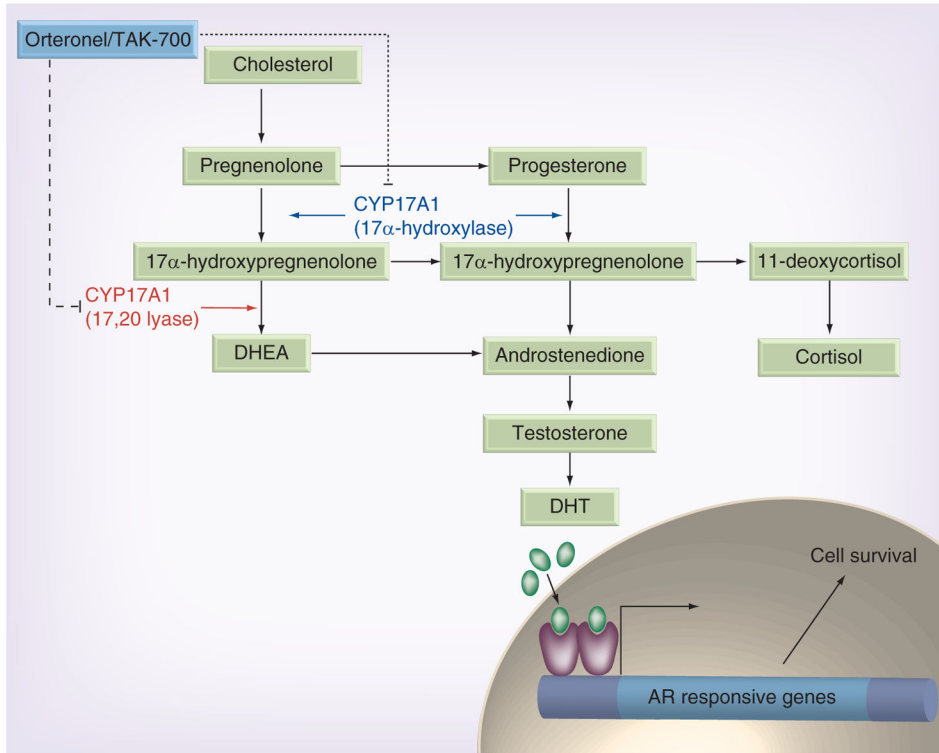
- Orteronel is an investigational drug under study in the treatment of metastatic prostate cancer (both androgen deprivation therapy [ADT]-naïve and castrate-resistant prostate cancer), as well as newly diagnosed, high-risk localized prostate cancer.
- Phase II studies are promising with evidence of androgen suppression and prostate-specific antigen responses in doses 300 mg twice daily  $\pm$  prednisone.
- Interim analysis of one Phase III trial (ELM-PC 5) did not meet the primary end point of improved overall survival in the postdocetaxel setting and was unblinded.
- Additional Phase III studies evaluating the role of orteronel in chemotherapy-naïve metastatic castrate-resistant prostate cancer, ADT-naïve metastatic prostate cancer and ADT-naïve, high-risk localized prostate cancer are ongoing.

### Safety & tolerability

- Fatigue and nausea were the most common adverse event in single-agent orteronel studies while the dose-limiting toxicity of orteronel in combination with docetaxel was febrile neutropenia. Severe adverse effects include: pneumonitis, febrile neutropenia (orteronel in combination with docetaxel) and dehydration. Overall, the most common adverse effects include: nausea, vomiting, fatigue, neutropenia (orteronel in combination with docetaxel), hypokalemia, anorexia and constipation.
- There are no reported specific drug–drug interactions at this time.
- Orteronel treatment appears to be well tolerated at doses of 300 and 400 mg twice daily.



**Figure 1.**  
Orteronel (TAK-700).



**Figure 2. Pathway of androgen production in castration-resistant prostate cancer**  
 The dashed line indicates potent inhibition by orteronel and the dotted line indicates weaker inhibition by orteronel. AR: Androgen receptor; DHEA: Dehydroepiandrosterone; DHT: Dihydrotestosterone.

**Table 1**

Orteronel (TAK-700) Phase I, II and III clinical trials.

Study (year)	Trial details	Outcome	Ref.
Dreicer <i>et al.</i> (2010)	Phase I/II in 26 men with metastatic CRPC	300 mg b.i.d. is well tolerated and lowers PSA and androgen levels	[17]
Petrylak <i>et al.</i> (2012)	Phase I with docetaxel in 14 men with metastatic CRPC ( 1 prior cycle of chemotherapy)	200 or 400 mg b.i.d. plus docetaxel/prednisone is safe and tolerable. 400 mg b.i.d. has androgen-lowering activity and was the recommended dose for a Phase II trial	[18]
Petrylak <i>et al.</i> (2013)	Phase II with docetaxel in 24 men with metastatic CRPC (chemotherapy naive)	Results for 400 mg b.i.d. plus docetaxel/prednisone at 3 months: 50% PSA decline: 72% 90% PSA decline: 28% Objective response rate: 56% Median time to PSA progression: 6.1 months Median time to radiographic progression: not reached	[19]
Agus <i>et al.</i> (2012)	Phase I/II in 97 men with metastatic CRPC (chemotherapy naive)	Four dose cohorts 300 mg b.i.d. effective with similar efficacy in PSA response, androgen-lowering activity and reduction in CTCs 50% PSA decline at 12 weeks: 63% (300 mg b.i.d.) 50% (400 mg b.i.d. plus prednisone) 41% (600 mg b.i.d. plus prednisone) 60% (600 mg q.d.) Objective response rate: 19%	[20]
George <i>et al.</i> (2012) <sup>†</sup>	Phase II of 38 men with nonmetastatic CRPC	300 mg b.i.d. without steroids reduces testosterone and PSA levels	[21]
Hussain <i>et al.</i> (2013) <sup>†</sup>	Phase II of 38 men with nonmetastatic CRPC	50% PSA decline at 3 months: 76% 50% PSA decline at 6 months: 45% Median PSA declined 83% Median time to PSA progression and progression-free survival: 13.8 months 1- and 2-year metastasis-free survival: 94 and 69%, respectively	[22]
Dreicer <i>et al.</i> (2014)	Phase III of 1099 men randomized 2:1 to orteronel/prednisone vs placebo/prednisone	Orteronel does not improve overall survival (HR: 0.886 [95% CI: 0.739–1.062]; p = 0.1898) Orteronel does improve radiographic progression-free survival (HR: 0.76 [95% CI: 0.653–0.885]; p = 0.00038)	[23]

<sup>†</sup> Same trial.

b.i.d.: twice daily; CRPC: Castrate-resistant prostate cancer; CTC: Circulating tumor cell; HR: Hazard ratio; PSA: Prostate-specific antigen; q.d.: Once daily.

**Table 2**

## Safety outcomes in clinical trials

Study (year)	Study details	Toxicities	Ref.
Dreicer <i>et al.</i> (2010)	Orteronel Phase I/II	Most common TEAEs were fatigue, nausea, constipation, anorexia and vomiting	[17]
Petrylak <i>et al.</i> (2012)	Orteronel plus docetaxel Phase I	DLT was grade 3 febrile neutropenia at 400 mg b.i.d. Most common grade 3 AEs were neutropenia, hyperglycemia, febrile neutropenia, infusion reaction and hyponatremia	[18]
Petrylak <i>et al.</i> (2013)	Orteronel plus docetaxel Phase II	Most common grade 3 AEs were neutropenia, fatigue, leukopenia and dehydration Two on-study deaths unrelated to treatment	[19]
Agus <i>et al.</i> (2012)	Orteronel Phase I/II	Most common AEs were fatigue, nausea and constipation. Most common grade 3 AEs were fatigue and hypokalemia	[20]
George <i>et al.</i> (2012) <sup>†</sup>	Orteronel Phase II	Most common grade 3 AEs were hypertension, dyspnea, fatigue, hypokalemia and pneumonitis	[21]
Hussain <i>et al.</i> (2013) <sup>†</sup>	Orteronel Phase II	Most common grade 3 AEs were hypertension, dyspnea, fatigue, hypokalemia and pneumonitis	[22]
Dreicer <i>et al.</i> (2014)	Orteronel Phase III	Most common AEs were nausea, vomiting and fatigue Most common grade 3 AEs were increased lipase, increased amylase and fatigue	[23]

<sup>†</sup> Same trial.

AE: Adverse event; b.i.d.: Twice daily; DLT: Dose-limiting toxicity; TEAE: Treatment-emergent adverse event.