Review Article

Genetic Polymorphisms and Pharmacotherapy for Prostate Cancer

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Abstract:
The therapeutic landscape of pharmacotherapy for prostate cancer has dramatically evolved, and multiple therapeutic options have become available for prostate cancer patients. Therefore, useful biomarkers to identify suitable candidates for treatment are required to maximize the efficacy of pharmacotherapy. Genetic polymorphisms such as single-nucleotide polymorphisms (SNPs) and tandem repeats have been shown to influence the therapeutic effects of pharmacotherapy for prostate cancer patients. For example, genetic polymorphisms in the genes involved in androgen receptor signaling are reported to be associated with the therapeutic outcome of androgen-deprivation therapy as well as androgen receptor-pathway inhibitors. In addition, SNPs in genes involved in drug metabolism and efflux pumps are associated with therapeutic effects of taxane chemotherapy. Thus, genetic polymorphisms such as SNPs are promising biomarkers to realize personalized medicine. Here, we overview the current findings on the influence of genetic polymorphisms on the outcome of pharmacotherapy for prostate cancer and discuss current issues as well as future visions in this field.

Key Words:
androgen metabolism, androgen receptor, genetic polymorphism, pharmacotherapy, prostate cancer

Introduction

Androgen-deprivation therapy (ADT) with or without first-generation anti-androgen agents has been the gold standard as primary pharmacotherapy for treatment-naïve prostate cancer (1). Recently, the therapeutic landscape of pharmacotherapy for prostate cancer patients has been greatly evolving. Second-generation anti-androgen agents such as enzalutamide, apalutamide, and darolutamide as well as the CYP17 inhibitor abiraterone have been developed for castration-resistant prostate cancer (CRPC) (2). Although these drugs were initially developed for the treatment of CRPC, enzalutamide, apalutamide, and abiraterone have expanded for use in hormone-sensitive prostate cancer (HSPC) (3). In addition, taxane chemotherapy (docetaxel and cabazitaxel) and radioisotopes (radium-223) have been applied for the treatment of CRPC, and docetaxel has been indicated for HSPC (2). Thus, multiple therapeutic options for CRPC and HSPC are available. Therefore, useful biomarkers to identify patients that are suitable candidates for these treatments are required to maximize the efficacy of pharmacotherapy.

Genetic polymorphisms are considered one of the most promising biomarkers for the realization of personalized medicine (4). Genetic polymorphisms are inter-individual differences in germline DNA and defined as differences in genomic sequences between individuals that occur at a frequency of 1% or more in a population. Most genetic polymorphisms are single-nucleotide polymorphisms (SNPs), and polymorphisms are also detected in repeated sequences such as microsatellites. SNPs are observed at a frequency of ~1 in 1000 nucleotides, and more than 2 million SNPs exist in the entire human genome. SNPs are classified into the following types according to their function: regulatory SNPs (rSNPs), which are located in promoter regions; coding SNPs (cSNPs), which are located in exons and cause an amino acid substitution; silent SNPs (sSNPs), which are located in an exon but do not cause an amino acid substitution; intron SNPs (iSNPs), which are located in introns; and genome SNPs (gSNPs), which are located in intergenic regions (Figure 1). Accordingly, rSNPs and cSNPs are likely to change gene expression and protein function, which results in functional and phenotypic differences, respectively. In addition, sSNPs and iSNPs may affect expression levels of genes. Conversely, gSNPs are speculated to not play a direct functional role, but these may serve as genomic
markers linked with distinct functional SNPs.

Genetic polymorphisms can cause various phenotypic differences through changes of expression and/or activity in the corresponding gene. Genetic polymorphisms are also associated not only with disease susceptibility but also with treatment outcomes. For example, a genetic polymorphism in UGT1A1 (UGT1A1*28 and UGT1A1*6), which encodes UDP-glucuronosyltransferase, decreases enzyme activity, and delays the metabolism of SN-38, the active metabolite of irinotecan, which results in a higher incidence of adverse events by irinotecan. A test for genetic polymorphisms in UGT1A1 has been approved in Japan for patients who will be treated with irinotecan chemotherapy. A SNP in Nudix hydrolase 15 (NUDT15), which encodes the enzyme involved in the metabolism of thiopurines, was shown to be useful in predicting adverse events of thiopurines. A test for genetic polymorphisms in NUDT15 was recently approved in Japan for patients who will be treated with thiopurines. Thus, the significance of testing genetic polymorphisms including SNPs in medical care has been growing.

Several genome-wide associated studies (GWASs) on prostate cancer susceptibility in large cohorts have been reported, showing the value of hundreds of SNPs with prostate cancer incidence. In addition, various studies have reported the significance of SNPs in the outcome of pharmacotherapy for prostate cancer. An association of genetic background such as race and family history with the outcome of prostate cancer has been shown, which suggests that genetic factors play an important role in pharmacotherapy. In this review, we provide an overview of the current findings on the influence of genetic polymorphisms in pharmacotherapy for prostate cancer and discuss current issues and future directions in this field.

**Genetic Polymorphisms and Primary ADT for HSPC**

Aberrant activation of androgen receptor (AR) signaling is one of the main causes by which prostate cancer acquires castration resistance. Therefore, polymorphisms in genes related to the AR pathway may affect the therapeutic efficacy of primary ADT through influencing AR signaling activity. To date, 63 SNPs in 49 genes have been reported to be associated with the outcome of primary ADT for HSPC (Table 1).

De novo androgen synthesis in prostate cancer cells is a major source of androgen under castrated condition during ADT and is shown to play an important role in the progression to CRPC. Multiple studies have indicated the association of SNPs in genes involved in androgen metabolism, including CYP17A1, CYP19A1, HSD3B1, HSD17B2, HSD17B3, HSD17B4, AKR1C3, and SRD5A2, with the outcome of ADT (Figure 2). For example, a cSNP (rs1047303, 1245A>C, N367T) in HSD3B1, which encodes 3β-hydroxysteroid dehydrogenase 1 (3β-HSD1), results in a variant of 3β-HSD1 with high activity, and the prognosis of carriers of this variant is poor. The prognostic impact of the cSNP (rs1047303) in HSD3B1 in the United States was validated in an Asian cohort, although variant carriers were rare in Asian patients (~15%) compared with Caucasian patients (~50%) (Table 2). The prognostic impact of the cSNP (rs1047303) in HSD3B1 was validated in primary ADT plus docetaxel for HSPC. In addition, the prognostic difference by another SNP (rs1856888) in HSD3B1 was also indicated. Ross et al. initially reported that the variant G allele in rs1856888 was associated with a low risk of disease progression among men in the United States; however, a recent study from the United States showed poor prognosis in patients carrying the variant G allele in rs1856888. Because of the strong linkage disequilibrium between the SNP (rs1047303 and rs1856888) in HSD3B1, the variant allele in the SNPs (rs1047303 and rs1856888) in HSD3B1 is likely to be associated with poor prognosis in patients treated with primary ADT. In a study on an iSNP (rs1870050) in CYP19A1, Ross et al. reported that the variant C allele in rs1870050 was associated with a higher risk of disease progression among men in the United States. However, two recent studies showed a low risk of progression and better prognosis among Asian men with the variant C allele in rs1870050. In addition, the prognostic significance of an rSNP (rs743572) in the 5′ untranslated region of CYP17A1 has been shown.

In addition to enzymes for androgen metabolism, the pump for androgens such as dehydroepiandrosterone (DHEA) and testosterone also plays a key role in the development of CRPC. In SNPs in SLCO1B3 and SLCO2B1 genes,
| Gene name | Function | rs number | Polymorphism types | Treatment | Validation | Reference |
|-----------|----------|-----------|--------------------|-----------|------------|-----------|
| CYP17A1   | Androgen metabolism | rs6162, rs743572 | sSNP, rSNP | ADT | Validated | (12) |
| CYP19A1   | Androgen metabolism | rs1870050, rs4775936 | iSNP | ADT | Almost validated | (12), (13), (14) |
| HSD3B1    | Androgen metabolism | rs1047303 | cSNP | ADT | Validated | (10), (11) |
|           | Androgen metabolism | rs1856888 | gSNP | ADT | Almost validated | (10), (11) |
| HSD17B2   | Androgen metabolism | rs4243229, rs7201637 | iSNP | ADT | Almost validated | (12) |
| HSD17B3   | Androgen metabolism | rs2257157 | iSNP | ADT | Almost validated | (13) |
| HSD17B4   | Androgen metabolism | rs7737181 | iSNP | ADT | Almost validated | (13) |
| AKR1C3    | Androgen metabolism | rs12529 | cSNP | ADT | Controversial | (15), (16), (17) |
| SRD5A2    | Androgen metabolism | rs523349 | cSNP | ADT | Validated | (18), (19) |
| SLC10A3   | Androgen transporter | rs1419917 | cSNP | ADT | Validated | (20) |
| SLC10A4   | Androgen transporter | rs1077858, rs1789693, rs12422149 | iSNP, gSNP | ADT | Validated | (21), (22) |
| GNRH2     | Androgen synthesis | rs6051545 | cSNP | ADT | Almost validated | (23) |
| SHBG      | Androgen-binding protein | rs6259 | cSNP | ADT | Controversial | (24), (25), (26) |
| AR        | Steroid receptor | CAG repeat | rs5522 | ADT | Almost validated | (27) |
| ESR1      | Steroid receptor | rs1062577, rs9508016 | rSNP | ADT | Almost validated | (28), (29) |
| NR3C2     | Steroid receptor | rs12030724 | iSNP | ADT | Validated | (30) |
| YB-1      | Transcription factor | rs11549465 | cSNP | ADT | Almost validated | (31) |
| HIF1A     | Transcription factor | rs2939244 | rSNP | ADT | Almost validated | (32) |
| AHRDC3    | Target gene of AR | rs554145, rs7830622 | rSNP | ADT | Almost validated | (33) |
| FLT1      | Target gene of AR | rs9508016 | rSNP | ADT | Almost validated | (34) |
| SKAP1     | Target gene of AR | rs6051445 | rSNP | ADT | Almost validated | (35) |
| FBX32     | Target gene of AR | rs16934641 | rSNP | ADT | Almost validated | (36) |
| BNC2      | Target gene of ER | rs3763763 | rSNP | ADT | Almost validated | (37) |
| TACC2     | Target gene of ER | rs2091778 | rSNP | ADT | Almost validated | (38) |
| ALPK1     | Target gene of ER | rs13088089 | rSNP | ADT | Almost validated | (39) |
| LSMAP     | Target gene of NFκB | rs2387084 | rSNP | ADT | Almost validated | (40) |
| CCL17     | Target gene of NFκB | rs223899 | rSNP | ADT | Almost validated | (41) |
| PSMD7     | Target gene of NFκB | rs2387084 | rSNP | ADT | Almost validated | (42) |
| M0N1B     | Target gene of NFκB | rs284924 | rSNP | ADT | Almost validated | (43) |
| GSTM3     | Antioxidant | rs7483 | cSNP | ADT | Validated | (44) |
| CAT       | Antioxidant | rs564250 | gSNP | ADT | Almost validated | (45) |
| SLC28A3   | Nucleoside transporter | rs56350726 | cSNP | ADT | Almost validated | (46) |
| LRP2      | Sterol and steroid transporter | rs6433107, rs3944004, rs830994, rs3707613, rs831003 | iSNP | ADT | Almost validated | (47) |
| EGF       | Growth factor | rs4444903 | rSNP | ADT | Almost validated | (48) |
| IRS2      | Growth factor | rs7986346 | gSNP | ADT | Almost validated | (49) |

(Table continued on next page)
Higher testosterone uptake in patients with the variant allele of the cSNP (rs1047303) in SLC01B3 was reported to be associated with poor prognosis after primary ADT (29, 30, 31, 32). Another SNP (rs1077858) in SLC02B1 was also associated with prognosis (30, 31). Thus, SNPs in the genes involved in androgen metabolism and uptake in prostate cancer cells play a key role in the progression of prostate cancer through persistent androgen synthesis in prostate cancer under castrated condition (Figure 3).

SNPs in other molecules related to the AR pathway were also shown to have prognostic impact after primary ADT. For example, the CAG repeat in AR correlated with prognosis, although null results were also reported (27, 28, 29, 30, 31, 32). In addition, the iSNP (rs12030724) in YB-1 that regulates YB-1 expression, which results in AR and AR variant expression, was also associated with the prognosis of Japanese men with advanced prostate cancer treated with primary ADT (39). The cSNP (rs7483, I224V) in GSTM3, which encodes an antioxidant enzyme, was also reported to be prognostic in Japanese patients with nonmetastatic and advanced prostate cancer treated with primary ADT (40).

### Genetic Polymorphisms and Treatment with Novel AR-pathway Inhibitors (ARPIs) for CRPC

Novel ARPIs such as enzalutamide, apalutamide darolutamide, and abiraterone have been demonstrate to improve survival in patients with CRPC (2). Because abiraterone is taken up into cells by OATP2B1, which is encoded by SLC02B1, and then metabolized by 3β-HSD and 5α-reductase, the therapeutic effect of abiraterone treatment may depend on the activities of the molecules involved in androgen metabolism and uptake (Figure 2) (27, 28). Recent reports showed that SNPs in genes involved in androgen metabolism and transport such as CYP17A1, HSD3B1, SRD5A2, and SLC02B1 correlate with the outcome of abiraterone treatment (Table 3). An rSNP (rs2486758, -362T>C) in CYP17A1 was associated with prognosis after abiraterone treatment (41). In addition, variant carriers of the cSNP (rs1047303) in HSD3B1 showed poor prognosis after treatment with ARPI (45, 46). The prognostic impact of the cSNP (rs1047303) in HSD3B1 for both primary ADT for HSPC as well as ARPIs for CRPC may be because of hyperactive androgen synthesis in variant carriers. The variant allele in HSD3B1 is expected to lead to increased conversion from abiraterone to the more potent delta-4-abiraterone (47). Accordingly, the cSNP (rs1047303) in HSD3B1 was
Figure 2. Gene function of single-nucleotide polymorphisms (SNPs) associated with therapeutic effects and adverse events of drug therapy. Underlined organs and treatments in parentheses mean target organ and treatment in which the gene function of SNPs is involved, respectively. ADT, androgen-deprivation therapy; ARPI, androgen receptor-pathway inhibitor.

Table 2. Outcome and Frequencies of the rs1047303 Variant Allele of HSD3B1.

| Outcome                                      | Variant carrier | Number | Frequency carrying a variant allele | Reference |
|----------------------------------------------|-----------------|--------|-------------------------------------|-----------|
| Prostate cancer susceptibility               | High            | 626    | 48% (AC/CC, US)                     | (62)      |
| Hereditary prostate cancer susceptibility     | High            | 98     | 53% (AC/CC, US)                     | (63)      |
| Prognosis in primary ADT                     | Poor            | 118/137/118 | 51% (AC/CC, US)                   | (64)      |
| Prognosis in primary ADT                     | Poor            | 102    | 53% (AC/CC, US)                     | (65)      |
| Prognosis in primary ADT                     | Poor            | 218    | 54% (AC/CC, US)                     | (66)      |
| Prognosis in Abiraterone                     | Insignificant   | 76     | 45% (AC/CC, US)                     | (67)      |
| Progression in primary ADT or ADT + Docetaxel| Poor in low volume | 475   | 53% (AC/CC, US)                     | (68)      |
| Prognosis in Ezalutamide or Abiraterone      | Poor            | 266    | 8% (CC, US/UK)                      | (69)      |
| Prognosis in Ezalutamide or Abiraterone      | Poor            | 547    | 15% (CC, Canada/Europe)             | (70)      |
| Prognosis in primary ADT                     | Insignificant   | 103    | 18% (AC/CC, China)                  | (71)      |
| Prognosis in primary ADT                     | Poor            | 104    | 9% (AC/CC, Japan)                   | (72)      |
| Prognosis in Abiraterone                     | Favorable       | 99     | 14% (AC/CC, Japan)                  | (73)      |

ADT, androgen deprivation therapy; UK, United Kingdom; US, United States
shown to be associated with comparable or better treatment efficacy of abiraterone (21), (64).

Interestingly, several genes are overlapping in association with the prognosis between primary ADT and ARPIs, which both target the AR pathway (Table 4). SNPs in CYP17A1 and YB-1 are associated with the outcome of primary ADT and ARPIs, although the SNPs in each gene are different. Furthermore, the cSNP (rs1047303) in HSD3B1, cSNP (rs523349) in SRD5A2, and SNPs (rs1077858, rs1789693, and rs12422149) in SLC02B1 were shown to be common prognosticators in both primary ADT for HSPC and ARPIs for CRPC. The prognostic and antitumor impacts of the cSNP (rs523349) in SRD5A2 and SNPs (rs1077858, rs1789693, and rs12422149) in SLC02B1 were consistent between primary ADT and abiraterone. Intriguingly, a variant allele in HSD3B1 (rs1047303) was differentially associated with prognosis in patients treated with abiraterone and other therapies. These findings suggest that HSD3B1 (rs1047303)

Figure 3. Schematic of molecules involved in androgen synthesis and uptake. The metabolisms surrounded by red, light blue, and blue are mainly processed in adrenal glands, prostate cancer, and both, respectively. OATP2B1 uptakes DHEA into prostate cancer cells. DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone.

Table 3. Genetic Polymorphisms Associated with the Prognosis of Patients with Castration-Resistant Prostate Cancer Treated with Androgen Receptor-Pathway Inhibitors.

| Gene name | Function | rs number | Polymorphism types | Treatment | Validation | Reference |
|-----------|----------|-----------|-------------------|-----------|------------|-----------|
| CYP17A1   | Androgen metabolism | rs2486758, rs10883783 | rSNP, iSNP | Abiraterone | Validated | (68), (69) |
| HSD3B1    | Androgen metabolism | rs1047303 | cSNP | Abiraterone (21), Abiraterone or Enzalutamide | Validated | (65), (66) |
| SRD5A2    | Androgen metabolism | rs523349 | cSNP | Abiraterone | (71) |
| SLC02B1   | Androgen transporter | rs1077858, rs1789693, rs14550074 | iSNP, iSNP, cSNP | Abiraterone | (72) |
| YB-1      | Androgen receptor regulator | rs12422149 | cSNP | Abiraterone | (73) |
| CYB5A     | CYP17A1 activity regulator | rs1790834 | iSNP | Abiraterone | (74) |
| TSPYL1    | CYP17A1 and CYP3A4 regulator | rs3828743 | cSNP | Abiraterone | (75) |
| SULT1E1   | Estrogen metabolism | Group 1 (rs3775777, rs4149534, rs10019305) | iSNP | Abiraterone | (77) |
|           |          | Group 2 (rs3775770, rs4149527, rs3775768) | iSNP | Abiraterone | (77) |

SNP, single-nucleotide polymorphism

DOI: 10.31662/jmaj.2021-0004
JMA Journal: Volume 4, Issue 2 https://www.jmaj.jp/
may be a promising marker to select appropriate combination therapy with ADT. Further studies on the prognostic impact of these SNPs will be important to evaluate candidates for personalized medicine.

**Genetic Polymorphisms and Taxane Treatment for CRPC**

The taxane docetaxel is widely used not only for prostate cancer but also for various cancers such as lung, uterine, and ovarian cancers. Many reports have demonstrated the relationship between genetic polymorphisms and the efficacy and adverse events of docetaxel therapy. Previous studies, including several in prostate cancer, reported associations between drug transport genes (ABCB1, ABCG2, SLCO1B3) or drug metabolism genes (CYP1B1, CYP2C8, CYP3A4, CYP3A5) with therapeutic efficacy or adverse events (Figure 2) (81). As shown in Table 5, the cSNP (rs1056836, 4326C>G, L432V) in CYP1B1 was associated with poor response and prognosis (82,83). In addition, SNPs in estrogen receptor 1 (ESR1) were also associated with treatment efficacy in prostate cancer (84). SNPs in ESR1 were reported to be associated with the outcome of primary ADT and taxane chemotherapy although the position of SNPs in ESR1 is different (Table 4). Then, SNPs in ESR1 may serve as a predictive marker for taxane chemotherapy, OATP1B3, which is encoded by SLCO1B3, plays a role in taxane uptake into cells and is involved in taxane resistance in prostate cancer cells. SNPs in SLCO1B3 may be associated with the treatment efficacy of taxane (85). However, a recent study showed comparable prognosis after cabazitaxel for CRPC between genotypes in SLCO1B3 (rs4149117) (86). Because prognostic impact in primary ADT has been shown (27,28,29), the cSNP (rs4149117) in SLCO1B3 may serve as a predictive marker in pharmacotherapy for prostate cancer.

**Current Research Issues and Future Prospects for Personalized Medicine**

The associations between multiple SNPs and therapeutic effects of pharmacotherapy for prostate cancer have been reported, as described above. However, to date, no genetic marker has been clinically utilized in pharmacotherapy for prostate cancer, which suggests potential issues as described in the following. While some SNPs have been reproducible in validation studies, others have not yielded consistent results across studies (Table 1, 3, 5). This may be because of racial differences in the frequency of genetic polymorphisms and linkage disequilibrium (a phenomenon in which there is a correlation between genetic polymorphisms in a population). To resolve this issue, multiple studies with large populations and meta-analysis studies are required. In addition, advances in technology such as artificial intelligence may serve as a breakthrough method to resolve the complex linkage disequilibrium among individuals.

Another problem is that the data in most study cohorts were retrospectively collected in daily practice. A daily clinical follow-up generally shows deviations from the strict follow-up schedule in a clinical trial. To improve the quality of data, collecting clinical data using a strict protocol is desirable to obtain more robust findings. In addition, most studies to date have focused on target genetic polymorphisms of individual genes. Because this method may miss useful SNPs, comprehensive methods such as GWAS are required. In addition, a single marker may be not enough for accurate predictive ability, and this may be overcome by using multiple SNPs. GWAS indicated that a single SNP generally provides only a modest (odds ratio, 1.1-1.5) increased susceptibility risk of prostate cancer, where polygenic risk score (PGS) using multiple risk SNPs was developed and validated (35,36). Therefore, the PGS approach would be useful to increase diagnostic ability.

Furthermore, the genes of SNPs associated with therapeutic outcome can be the cause of treatment resistance. Therefore, these genes are promising targets to overcome treatment resistance. Genes involved in androgen metabolism such as CYP17A1, HSD3B1, AKR1C3, and SRD5A2 have been candidate targets for drug discovery and drug development, and the SNPs may be crucial in therapeutic efficacy (Table 6).

**Conclusion**

Here, we summarized the known associations between genetic polymorphisms and the outcomes of pharmacotherapy in prostate cancer patients. Recently, multiple novel therapeutic options for HSPC have emerged, and the stratification of suitable patients for each option will be required. Genetic biomarkers such as SNPs will be beneficial for stratifying patients and for estimating the treatment response of an individual patient. The combination of genetic biomarkers with traditional clinicopathological parameters could improve the prognostication and the choice of the most appropriate treatment for each patient, which will be helpful in clinical decision making. Thus, personalized medicine using genetic biomarkers is expected to be realized in pharmacotherapy for prostate cancer. However, unresolved issues remain, such as inconsistent results among studies as well as the current lack of GWAS and PGS approaches, and these issues should be addressed in future research.

**Article Information**

This article is based on the study, which received the Medical Research Encouragement Prize of The Japan Medical Association in 2020.

**Conflicts of Interest**

Masaki Shiota received honoraria from Janssen Pharmaceutical Company, Astellas Pharma, and Sanofi; Shusuke Akamat-
| Gene name | rs number | Treatment regimen | Risk allele | Outcome | Reference |
|-----------|-----------|-------------------|-------------|---------|-----------|
| CYP17A1   | rs6162    | ADT               | G           | OS      | (12)      |
|           | rs743572  | ADT               | A           | OS      | (13)      |
|           | rs2486758 | Abiraterone       | C           | PFS     | (14)      |
|           | rs10883783| Abiraterone       | A           | PFS     | (15)      |
|           | rs1047303 | ADT               | C           | PFS, MFS, OS | (16) |
|           | rs1856888 | ADT               | A           | PFS     | (17)      |
| HSD3B1    | rs1047303 | ADT               | C           | PFS     | (18)      |
|           | rs1856888 | ADT               | A           | PFS     | (19)      |
| SRD5A2    | rs523349  | ADT               | G           | PFS, OS | (20)     |
|           |           | Abiraterone       | G           | PFS     | (21)      |
| SLCO1B3   | rs4149117 | ADT               | T           | OS      | (22)      |
|           |           | T                 | T           | CSS     | (23)      |
|           |           | Calazitaxel       | Null        | OS      | (24)      |
| SLCO2B1   | rs1077858 | ADT               | G           | PFS     | (25)      |
|           |           | G                 | T           | PFS     | (26)      |
|           |           | Abiraterone       | T           | MRD     | (27)      |
|           | rs1789693 | ADT               | T           | PFS     | (28)      |
|           | rs34550074| Abiraterone       | T           | MRD     | (29)      |
|           | rs12422149| ADT               | A           | CSS     | (30)      |
|           |           | ADT               | G           | PFS     | (31)      |
|           |           | ADT               | G           | PFS     | (32)      |
|           |           | Abiraterone       | G           | PFS     | (33)      |
| YB-1      | rs10493112| Abiraterone       | A           | PFS     | (34)      |
|           | rs12030724| ADT               | A           | PFS     | (35)      |
| ESR1      | rs1062577 | ADT               | A           | OS      | (36)      |
|           | rs2234693 | Docetaxel         | C           | PFS     | (37)      |
|           | rs9340799 | Docetaxel+Thalidomide | G | PFS | (38) |

ADT, androgen deprivation therapy; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival
Table 5. Genetic Polymorphisms Associated with the Outcome of Taxane Treatment for Castration-Resistant Prostate Cancer.

| Gene name | Function                  | rs number                | Polymorphism types | Treatment                                      | Validation | Reference |
|-----------|---------------------------|--------------------------|--------------------|------------------------------------------------|------------|-----------|
| CYP1B1    | Drug metabolizing enzyme  | rs1056836                | cSNP               | Docetaxel                                      | Validated  | (82), (83) |
| ABCB1     | Drug excretion pump       | rs1128503, rs2032582,    | cSNP, iSNP         | Docetaxel+Thalidomide                          |            | (84)      |
| ABCB1I    | Drug excretion pump       | rs7602171                | iSNP               | Docetaxel+Thalidomide                          |            | (85)      |
| ABCG2     | Drug excretion pump       | rs2231142                | cSNP               | Docetaxel+Vinorelbine/Vinblastine/Estramustine |            | (86)      |
| ESR1      | Steroid receptor          | rs2234693, rs9340799     | iSNP               | Docetaxel+Thalidomide                          |            | (87)      |
| GSTP1     | Antioxidant               | rs1138272                | cSNP               | Docetaxel+Thalidomide                          |            | (88)      |
| SLC5A6    | Transporter               | rs1395                   | cSNP               | Docetaxel+Thalidomide                          |            | (89)      |
| VEGFA     | Angiogenesis              | rs1570360                | rSNP               | Docetaxel, Celecoxib + Cyclophosphamide        |            | (90)      |

SNP, single-nucleotide polymorphism

Table 6. Druggable Targets in Androgen Metabolism and Their Inhibitors.

| Target enzyme | Inhibitor                              | Developmental status                      |
|---------------|----------------------------------------|-------------------------------------------|
| CYP17         | Abiraterone                            | Approved                                  |
|               | Orteronel (TAK-700)                    | Phase III (terminated)                    |
|               | Galetterone                            | Phase II (terminated)                     |
| 3β-HSD        | Trilostane                             | Phase II (terminated)/on market for Cushing’s syndrome |
| AKR1C3        | Indometacin                            | Phase II/on market as NSAIDs              |
|               | N-(indolylcarbonyl)-piperidines        | Phase I                                   |
| 5α-reductase (types I and II) | Dutasteride                            | Phase II (terminated)/on market for benign prostatic hyperplasia |
| 5α-reductase (type II)  | Finasteride                            | On market for androgenetic alopecia       |

NSAID, non-steroidal anti-inflammatory drug

Sources of Funding
This work was supported by Takeda Science Foundation and Japanese Urological Association to Masaki Shiota.

Acknowledgement
We thank Gabrielle White Wolf, PhD, from Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

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