Genomic Profiling in ctDNA Revealing Complicated Resistance Mechanism of Olaparib and Abiraterone as Salvage Therapy in Prostate Cancer: A Case Report

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Case Report

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Abstract

Background: PARP inhibitor, e.g. Olaparib, displayed superior clinical effect in metastatic castration prostate cancer (mCRPC) patients with deleterious mutations of DNA damage repair genes (DDR) as reported recently. Besides, for mCRPC patients without DDR alterations, a combination of Olaparib and abiraterone may achieve an acceptable clinical outcome as indicated by researches. However, these previous clinical studies involved patients strictly following inclusion criteria. In real-world situations, where the situation of patients is more complicated, the efficacy of salvage treatment of Olaparib with or without abiraterone-prednisone remains to be unclear.

Case presentation: The present case displayed a 61-year-old man who was initially diagnosed with metastatic hormone-sensitive prostate cancer(mHSPC) and proceeding into mCRPC after several kinds of standard therapies. Surprisingly, the patient had a well TPSA response and remission of symptoms for four months by taking Olaparib combined with abiraterone-prednisone, basing on androgen-deprivation therapy (ADT). The resistance of Olaparib was occurred with slowly increasing serum TPSA level again.

Conclusion: Resistance mechanism as discovered by comprehensive genomics profiling. The major concern was that two somatic reversion mutations occurred in *PALB2* recovering its reading framer storing the function of the primary *PALB2* mutation and caused the resistance to a PARP inhibitor.

Background

Prostate cancer is sixth mostly occurred malignant tumor in the mainland China[1]. Patients with metastatic castration prostate cancer (mCRPC), as the most dangerous subtype, often have an unfavored clinical outcome as well as poor life quality[2]. Therapeutic options when progressing to mCRPC are limited besides the administration of second-generation androgen receptor inhibitor, abiraterone or docetaxel together with prednisone, based on androgen-deprivation therapy (ADT).Poly (ADP-ribose) polymerase (PARP) inhibitor displayed promising clinical performance and prolonged survival duration, life quality in HRR gene mutated patients with ovarian cancer[3], breast cancer[4], pancreatic cancer[5] and prostate cancer[6, 7]. Recent studies showed potential clinical efficacy of Olaparib in mCRPC patients, especially carrying deleterious mutations of DNA damage repair (DDR) genes. Among these genes, *BRCA2* deleterious mutation may serve as an appropriate indicator for the response to PARP inhibitor. Lately released results from PROfound study[8] also indicated a promising clinical outcome when patients with *BRCA1/2* or *ATM* deleterious mutations receiving Olaparib treatment. Meanwhile, for patients without DDR deleterious mutations, a combination of Olaparib together with abiraterone-prednisone may be used as an optimal therapeutic approach[9]. However, clinical trials involved patients strictly following inclusion criteria. Therefore, in a real-world situations, where the status of patients is more complicated, the efficacy of salvage treatment of Olaparib with or without abiraterone mains to be unclear.

Case Presentation

A 61-year-old man went to our hospital due to continuous lumbosacral pain for three months. The magnetic resonance imaging (MRI) of the lumbar vertebrates showed multiple bone space-occupying lesions (Fig. 1a). Bone scanning further displayed the high metabolic activity of these lesions (Fig. 1b). MRI of the prostate indicated invasion of the seminal vesicle, bladder wall, and metastasis to pelvic lymph node (Fig. 1c). No special aberration was found in the lung. Together with a significantly increased level of serum total prostate-specific antigen (TPSA, 787 ng/ml) and normal level of neuron-specific enolase (NSE, 4.32 ng/ml), an ultra-sound guided transperineal prostate needle biopsy (altogether 14 needles) was conducted resulting in confirmed diagnosis of prostate adenocarcinoma with the highest Gleason score (5 + 5 = 10) and extreme positive rate (14/14). Immunohistochemistry (IHC) staining on serial sections of biopsy tissue excluded neuro-endocrine component [CK-L(+), PSA(+), P504S(+), NKX3.1(+), AR(++) > 95%, P63(-), CK34βE12(-), Syn(-), CgA(-), CD56(-), ki-67 30%(+)] (Fig. 1d). Thus, this patient was definitely and initially diagnosed with metastatic hormone-sensitive prostate cancer (mHSPC, pT4N1M1b, stage IV).

797Therefore, ADT in combination with docetaxel was applied as initial treatment[10–12], especially for mHSPC with high tumor burden[13]. Two cycles of therapeutic intervention significantly relieved patient-reported pain as well as TPSA level dropped to 0.45 ng/ml (Fig. 2b). Due to severe bone marrow inhibition and liver toxicity, docetaxel was no longer administrated, but continuing androgen-deprivation therapy. Lumbosacral pain manifestation along with a bounce of increased TPSA was observed after 5 months, meanwhile testosterone levels remained castrated throughout, which indicated his disease progressed to mCRPC. To determine primary resistance and sensitivity for new endocrine therapy, we tested the number and classification of circulating tumor cells (CTCs) together with AR-V7 mRNA in these CTCs[14] (Method see Additional file 1). Based on the negative findings on the detection, we confidently decided to choose the abiraterone-prednisone administration for his maintenance therapy (Fig. 2a). Decreased TPSA level (3.02 ng/ml) was measured at the 6th month of treatment. Fortunately, the disease was effectively controlled by abiraterone for nearly one year. Elevated TPSA level (69.57 ng/ml) indicated the second time of disease progression. Increased number of CTCs along with overexpression of AR-V7 mRNA further confirmed abiraterone resistance (Fig. 2a-b). The patient was eligible for a phase III multicenter, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of Proxalutamide (an AR antagonist) in patients with metastatic castration-resistant prostate cancer (mCRPC) who failed abiraterone acetate and docetaxel (The trial is not over yet). Unfortunately, the disease progressed rapidly, reflected in the increased TPSA level (601 ng/ml) along with severe bilateral lower limb edema and the presence of somnolence. Due to no germline *BRCA1/2* deleterious mutation detected from his peripheral blood mononuclear cell at the first time of genetic testing, the tumor was re-challenged by abiraterone together with a PARP inhibitor, Olaparib. TPSA decreased rapidly and amazingly to 119.65 ng/ml from 601.61 ng/ml after one month's combined treatment and maintained at a very low level (8.02 ng/ml) (Fig. 2c). ECOG performance and mental state were significantly improved with decreased painful feelings as well as lowering morphine dosage. After five months of' clinical response to this combinational therapeutic regimen, TPSA climbed with increasing patient-reported carcinomatous pain and decreasing ECOG performance. When the disease progressed again,

comprehensive genomic profiling for his ctDNA was performed. 508 cancer-related genes were sequenced by next-generation sequencing (Method see Additional file 1). *PALB2* germline pathogenic mutation was unclosed. Meanwhile, 12 somatic variants as well as 3 copy number alterations were detected in following genes (*PTEN, AR, CHD1, TP53, FGFR1, NOTCH2, PIK3C2G, LHCGR, CDC25C, FLT4)* and especially two reverse missense mutations in *PALB2* which may recover truncated poly-peptide chain translated from germline *PALB2* mutation (Fig. 3, Table 1). In detail, two somatic mutations of *PALB2*, c.751_752delCAinsTT and c.751_753delCAGinsTAC (Fig. 3), shared same loci with the germline deleterious variant c.751C > T. As a result, missense mutations led by these two in-frame deletion or insertion variants contributed to restore entire *PALB2* reading frame and to make its function correctly in repairing DNA double-stranded breaks by homologous recombination repair pathway. Besides these two reversed mutations of *PALB2*, ctDNA profiling discovered a complicated resistance mechanism to the combinational therapy of Olaparib and abiraterone in this patient via activation of multiple signaling pathways.

Table 1
Summary of genomic alterations in ctDNA detected from the patient with resistance of Olaparib.

Gene	Base change	Amino acid variation	Exon	Variant frequency	Transcript
PTEN	c.136_137del	p.Y46Qfs*5	EX2	59.47%	NM_000314.4
AR	Copy number gain				
CHD1	Copy number loss				
FGFR1	Copy number gain				
TP53	c.665_672*11del	-	EX6-IVS6	36.13%	NM_000546.5
NOTCH2	c.5311-1G□A	-	IVS29	1.28%	NM_024408.3
PIK3C2G	c.2143A□G	p.R715G	EX15	40.23%	NM_004570.4
LHCGR	c.143C□T	p.T48M	EX1	23.39%	NM_000233.3
PALB2	**c.751_752delCAinsTT**	**p.Q251L**	**EX4**	**7.31%**	**NM_024675.3**
PALB2	**c.751_753delCAGinsTAC**	**p.Q251Y**	**EX4**	**3.79%**	**NM_024675.3**
PALB2	**c.751C□T**	**p.Q251***	**EX4**	**germline**	**NM_024675.3**
CDC25C	c.1150_1151delGGinsCC	p.G384P	EX12	2.35%	NM_001790.3
FLT4	c.376G□A	p.A126T	EX3	1.15%	NM_002020.4

Bold texts show the three PALB2 mutations of the patient.

Indeed, functional assays are needed to validate resistant mechanisms indicated by these ctDNA findings.

Discussion

Patients were considered to be short-lived when developed to mCRPC, despite significant progress in systemic and anti-androgen therapy. In this case, a mHSPC patient received multiple lines of therapy, and an acceptable clinical response to Olaparib and abiraterone-prednisone combination therapy was achieved. Genetic testing of ctDNA indicated a complicated mechanism for his final disease progression.

Previous studies reported the vital contribution of the alternative splice of AR-V7 to resistance to anti-androgen therapy[15, 16]. In our case, when developed to mCRPC, CTCs and AR-V7 mRNA testing were negative. This patient had a nearly one-year progression-free interval receiving abiraterone mono-therapy, basing on testosterone levels that remained castrated throughout the entire process. Disease progression was mainly due to a secondary AR-V7 overexpression as well as the epithelial-mesenchymal transition of prostate cells as in parallel with reported investigations[17]. In addition, androgen receptor amplification or gain of function mutations of AR, as observed in ctDNA of this patient, would also continuously activate downstream AR signaling pathway overcoming extrinsic androgen inhibition[18, 19].

Recent progress delineated a subgroup of prostate patients, especially the loss of function mutations of *BRCA2* gene, benefiting from the treatment of PARP inhibitors. In TOPARP-A and TOPARP-B study [6, 7], Olaparib mono-therapy has antitumor activity against mCPRC with HRR or DDR gene alterations. TOPARP-B study showed *BRCA1/2* mutated mCRPC patients yielded an objective response rate of 83.3%. Recently released results from PROfound study showed that Olaparib provided a statistically significant and clinically meaningful improvement on BICR assessed rPFS, especially for *BRCA2*-mutated patients[8]. A similar benefit was observed in TRITON2 (rucaparib)[20, 21] and GALAHAD (niraparib) study[22].

Neither germline *BRCA2* nor *BRCA1* deleterious mutation was found in this patient as shown by the first genetic testing. Supported by the conclusion from study 08[23], Olaparibin combination with abiraterone showed significant clinical benefit and this efficacy lasted for nearly five months. Progression was inevitably occurred, which led to the second time of genetic testing. Comprehensive genomic profiling uncovered that, instead of *BRBA1/2*, this patient had a germline *PALB2* nonsense mutation which may lead to truncation of PALB2 protein. As this patient was resistant to prior abiraterone treatment together with AR amplification and AR-V7 overexpression, abiraterone may not be able to block AR signaling triggering “BRCAness”[24]. PALB2, as one of tumor suppressor genes, by physically interacting with BRCA2 followed by recruiting RAD51 to DNA breaks, plays critical roles in repairing DNA double-strand breaks by homologous recombination (HR)[25]. A couple of studies indicated *PALB2* deleterious mutations were associated with clinical benefit from PARP inhibitors[6, 20]. For instance, TOPARP-B study showed patients with *PALB2* germline or somatic loss of function mutation may benefit from Olapraib treatment[6].

This patient had disease worsened after five months’ disease relieving period, which indicated PARP inhibitor resistance. The most known mechanism is the secondary somatic reverse mutation in germline mutated genes. Goodall et al reported in a mCRPC patient with germline *PALB2* p.L253Ifs*2, who had a 9-month clinical benefit from Olaparib and two reverse somatic mutations in *PALB2* were detected in his

ctDNA at disease progression[26]. In our case, this patient had a germline *PALB2* p.Q251* nonsense mutation. Two somatic reverse mutations which may restore *PALB2* reading frame were observed when the disease progressed.

Besides reverse mutation as a potential mechanism on PARP inhibitor resistance, EwaGogola et al[27] concluded four major mechanisms of PARP inhibitor resistance including upregulation of drug efflux, restoration of homologous recombination, target-specific resistance to PARP inhibitor and restoration of stalled replication fork protection. Meanwhile, by the genomic profiling, we proposed restoration of homologous recombination was not only induced by reverse mutations of *PALB2*. Loss of function mutation of *PTEN* together with *FGFR1* amplification may directly and indirectly activated PI3K-AKT-mTOR as well as RAS-RAF-MAPK/ERK signaling pathway[28]. Activation of these oncogenic pathways may further drive the expression of HR genes compensating DNA double breaks. In addition, activation of these signaling pathway may accelerate cell-cycle and evade apoptosis[29]. In this case, the mechanism of PARP inhibitor resistance was explored in detail via comprehensive genomic profiling. Further validation at the functional level is warranted.

Several therapeutic issues need to be concerned. Firstly, as fully respecting patient's willingness, comprehensive genomic profiling can only be performed when the resistance of Olaparib occurred. In this circumstance, it could not distinguish the primary or secondary source of these two somatic *PALB2* mutations. Secondly, therapeutically, instant multiple gene testing is definitely essential. Detection of germline *PALB2* aberration at a relatively early stage may make this patient receive Olaparib mono-therapy, but not being enrolled into the Proxalutamide clinical trial. Thirdly, *PALB2* is a cancer susceptibility gene that may be increasing the risk of breast cancer as well as be substantially associated with the onset of ovarian cancer, pancreatic cancer and male breast cancer[30]. Concerning this patient carried a *PALB2* germline pathogenic variation, his first and secondary degree relatives need to visit a genetic counselor for further evaluation.

Conclusion

Here we described a complete treatment period of a prostate cancer patient from mHSPC to mCRPC till death because of disease progression. Endocrine therapy, chemotherapy, and the target therapy utilizing PARP inhibitor as well as abiraterone were chosen. The prostate cancer with HRR gene mutation may be more sensitive to the PARP inhibitor, but we should also realize the occurrence of the resistance to the PARP inhibitor, such as the somatic reverse mutation. We also recommend that timely multi-gene testing is of great importance for patients, especially mCRPC, to select a precise therapeutic approach.

List Of Abbreviations

mCRPC: metastatic castration prostate cancer; DDR: DNA damage repair; mHSPC: metastatic hormone-sensitive prostate cancer; ADT: androgen-deprivation therapy; PARP: Poly (ADP-ribose) polymerase.

Declarations

Ethics approval and consent to participate

Acquisition of tissue specimens and genomic analyses were approved by the Ethics Committee of Chongqing University Cancer Hospital,Chongqing,China.

Consent for publication

Written informed consent was obtained from the patient and his wife for the publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials

The dataset supporting the conclusions of this article is included with in the article and its additional file 1.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Fang Yuan and Nan Liu contributed equally as co-first authors in collecting clinical data and writing the paper; Fang Yuan and Hong Luo provided clinical treatment; Xiaotian Zhang performed the molecular genetic studies; Mingzhen Yang and Hong Zhou designed and coordinated the study and participated in draft preparation. The authors read and approved the final manuscript.

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Figures

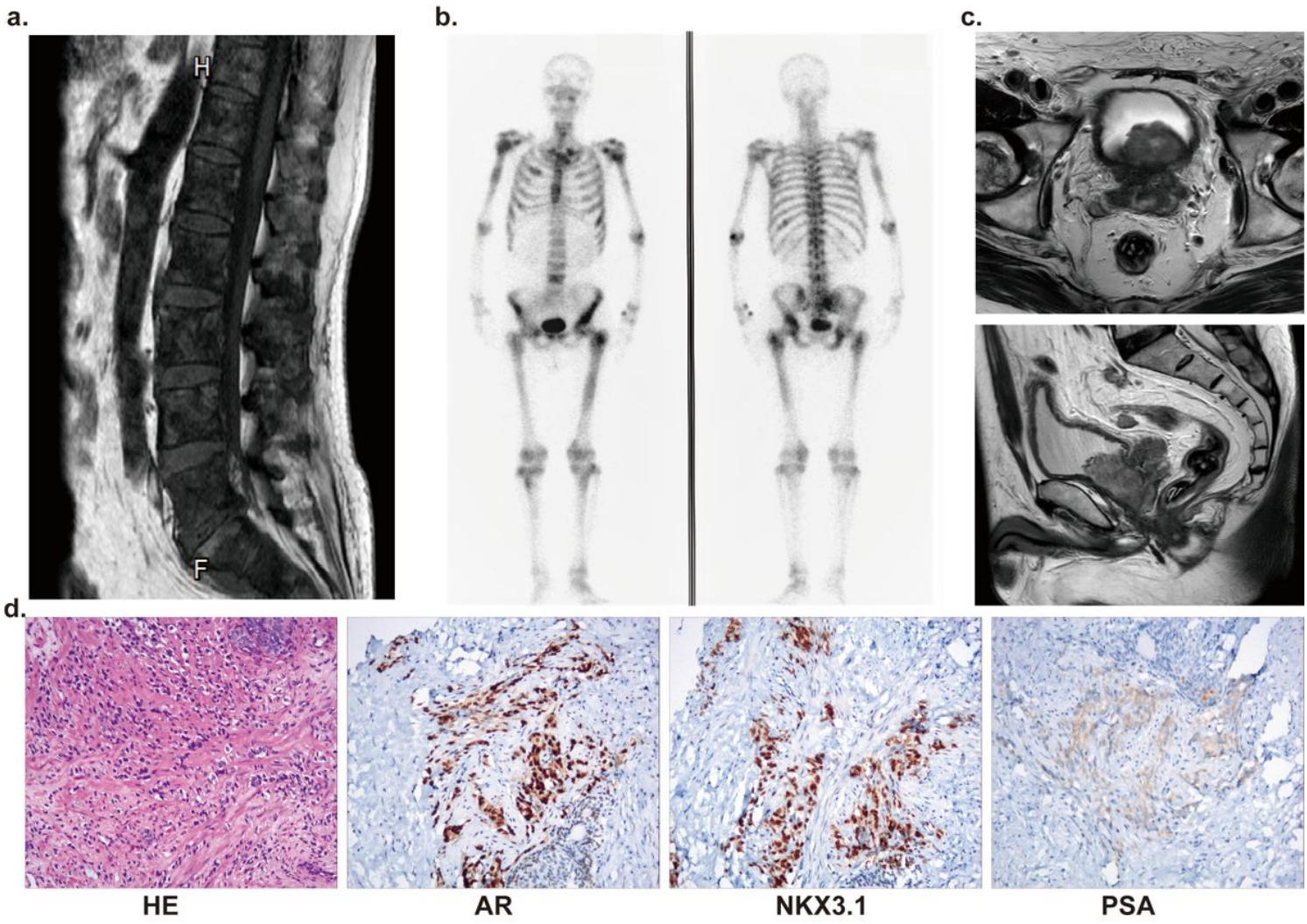


Figure 1

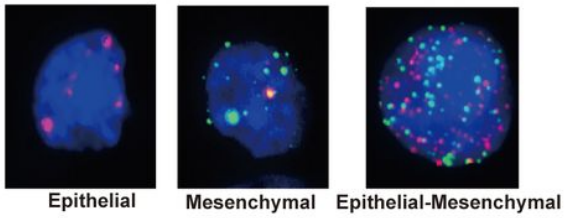
Radiological and immunohistochemical results showing metastatic prostate adenocarcinoma. a: Sagittal MRI showed multiple lumbar vertebrate metastasis. b: Bone scanning displayed highly metabolic activity of bone lesions. c: Cross (upper) and sagittal (lower) section of MRI scanning displayed bladder wall as

well as seminal vesicle invasion of prostate malignant lesion. d: H&E staining and immunohistochemistry resulted for AR, NKX3.1 and PSA staining.

a.

Circulating	/counts	EMT-CTC /counts	M-CTC /counts	CTC clusters /counts	AR-V7 mRNA expression
2017-06-13	1	6	0	0	Negative
2018-06-19	1	15	11	0	Positive

b.



c.

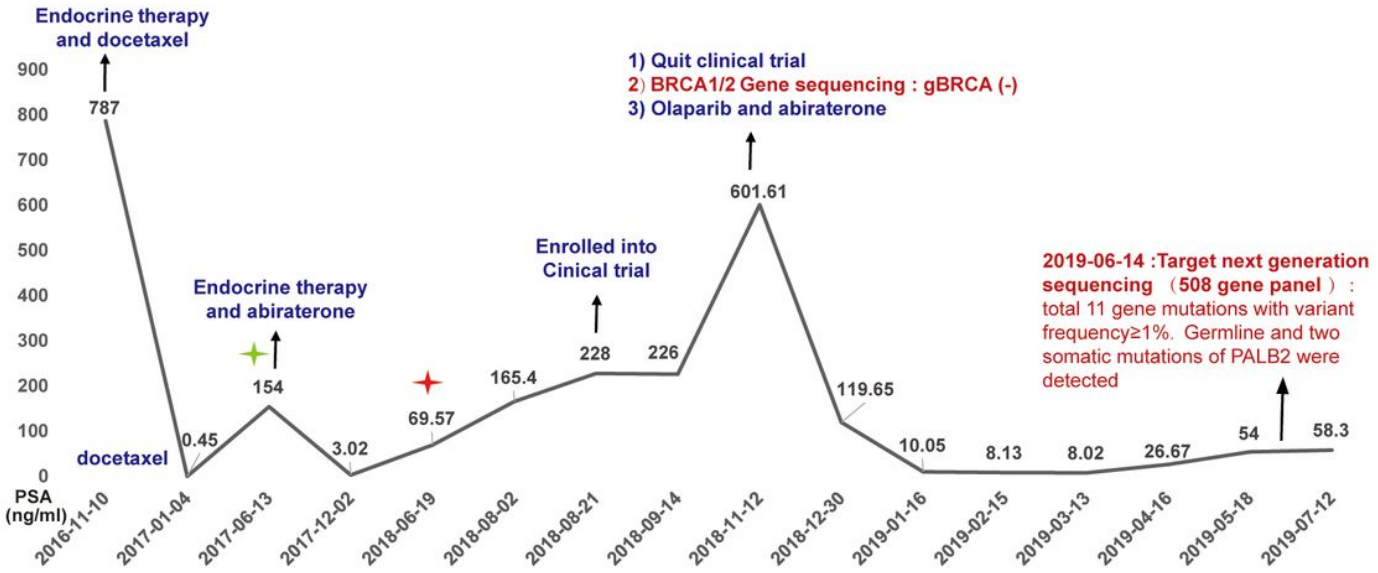


Figure 2

Results of CTCs detection and dynamic change of TPSA level. a: CTCs counts and classification change before and after abiraterone treatment, the expression of AR-V7 mRNA in these CTCs were detected. b: Representative graphs displaying CTCs of three phenotypes. Red signal: Probe mixture detecting mRNA of EpCAM,CK8, CK18, CK19; Green signal: Probe mixture detecting mRNA of Vimentin and Twist. c: Dynamic change of TPSA level during overall treatment procedure with various therapeutic approaches.

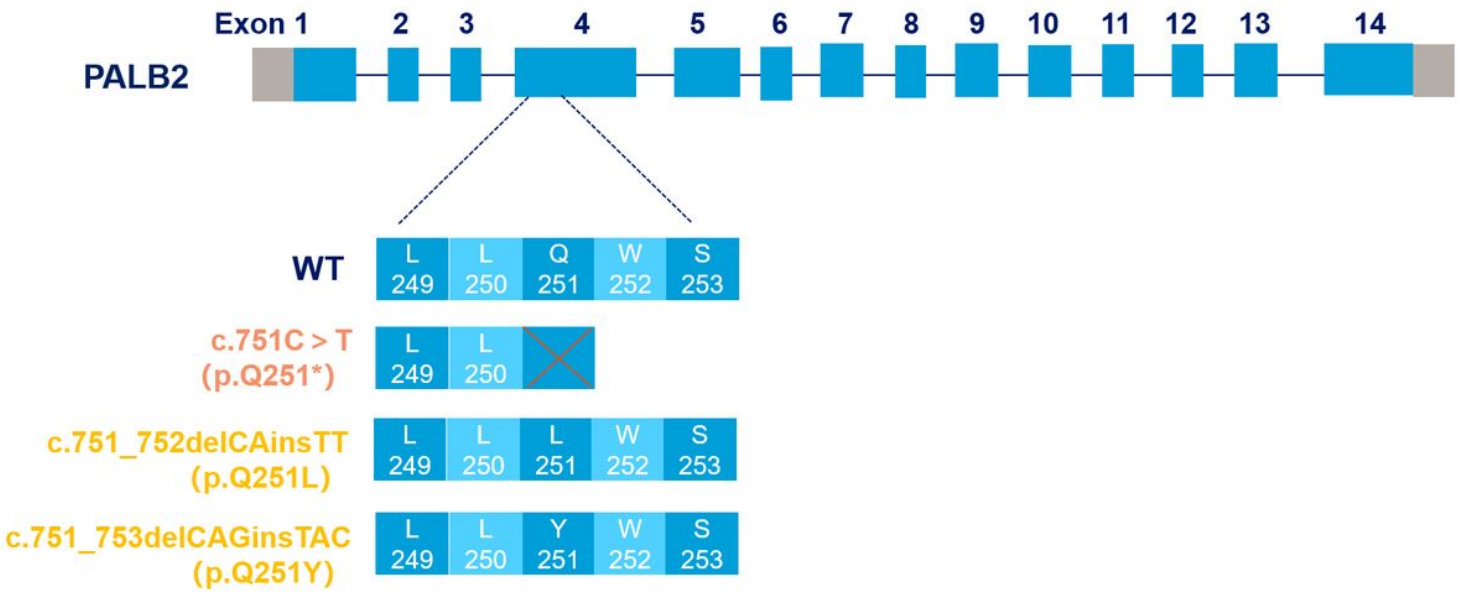


Figure 3

Diagram of PALB2 amino-acid sequence changes caused by the germlinemutation and two somatic mutations.

Supplementary Files

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