

P-2019/46551

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIRECCIÓN DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. **NC2019/0011591**Solicitud de patente a nombre de **JANSSEN PHARMACEUTICA NV.**

Yo, CAROLINA DAZA MONTALVO identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53, obrando como apoderada de la sociedad JANSSEN PHARMACEUTICA NV., domiciliada en Monheim am Rhein, Alemania, solicitante de la patente de la referencia, en respuesta al oficio No. **4053** notificado electrónicamente el 25 de marzo de 2022, relacionado con los requerimientos de fondo de la solicitud, y para el cual se solicitó prórroga de 30 días el 17 de junio de 2022, atentamente me permito presentar la siguiente información:

1. Modificaciones a las Reivindicaciones y Claridad

Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial nuevo capítulo reivindicatorio, el cual consta de ocho (8) reivindicaciones y reemplaza completamente el capítulo presentado anteriormente. Específicamente, se realizaron las siguientes modificaciones:

1.1 Se han modificado las antiguas reivindicaciones 1 a 5 para eliminar lo relacionado a las composiciones farmacéuticas con prednisona o prednisolona.

1.2 Se han adicionado las nuevas reivindicaciones 6 a 8 relacionadas a las composiciones farmacéuticas con prednisona o prednisolona.

1.3 Se eliminaron las antiguas reivindicaciones 6 a 12.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones de claridad y patentabilidad planteadas por el examinador en su concepto técnico.

En consecuencia, nos permitimos indicar que el presente capítulo reivindicatorio, que incluye ocho (8) reivindicaciones, se ajusta a las disposiciones del artículo 30 de la Decisión 486/00.

2. Pago de tasas

En relación con el número de reivindicaciones, atentamente nos permitimos decir que no se adjunta tasa por concepto de reivindicaciones adicionales, toda vez que el nuevo capítulo reivindicatorio tiene un menor número de reivindicaciones a las presentadas previamente, y en esencia es el mismo objeto, pero definido con mayor claridad.

Por otra parte, me permito adjuntar recibo por concepto de pago de tasa de modificación a las reivindicaciones, según lo establecido en la **Resolución No. 59669 de 2020**.

3. Unidad de Invención

El examinador ha indicado que *"La solicitud carece de unidad de invención, debido a que reclama más de un grupo inventivo sin la presencia de características o elementos técnicos nuevos e inventivos que son comunes a todas las invenciones, lo anterior, teniendo en cuenta que el concepto común es composiciones para el tratamiento farmacológico de cánceres de próstata resistente a hormonas, de alto riesgo y resistentes a la castración, y se encuentra divulgado en el estado de la técnica, específicamente en el documento Ensayo NCT01576172 (Brazos e intervenciones).*

Por lo tanto, esta invención presenta diferentes conceptos técnicos inventivos así:

- *Grupo inventivo 1: Una composición farmacéutica que comprende niraparib y acetato de abiraterona (reivindicaciones 1 a 5).*
- *Grupo inventivo 2: una composición farmacéutica que comprende prednisona o prednisolona (reivindicaciones 1 a 10).*
- *Grupo inventivo 3: Una composición farmacéutica que comprende niraparib (reivindicaciones 6 a 10).*
- *Grupo inventivo 4: Una composición farmacéutica que comprende acetato de abiraterona (reivindicaciones 6 a 10).*

(...) Por consiguiente, la búsqueda del estado de la técnica y el examen de patentabilidad fueron realizados para el primer grupo inventivo citado”.

En este respecto, el solicitante desea manifestar respetuosamente su desacuerdo con dicha objeción. Sin embargo, se informa que la invención se limita al **Grupo Inventivo 1** referido en el Oficio que se contesta. Por lo tanto, se ve superada dicha objeción y se cumple con el requisito de patentabilidad.

Adicionalmente, se informa que el solicitante se reserva el derecho de presentar una o más divisionales durante el trámite.

4. Nivel Inventivo

El examinador establece que las reivindicaciones 1 a 5 carecen de nivel inventivo a la luz de las enseñanzas descritas en los documentos Ensayo NCT01576172, National Cancer Institute (NCI) (D2), y Sandhu S. K., *et al. The lancet oncology* (D3).

A este respecto, me permito decir que el artículo 18 de la Decisión 486 establece que *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”.*

Lo anterior significa que el análisis de nivel inventivo **NO** es una comparación de los objetos de las anterioridades y la solicitud en estudio. El análisis de nivel inventivo **debe demostrar** la obviedad de la invención y establecer cómo ésta no contiene un salto cualitativo, que demuestre su altura inventiva, teniendo en cuenta que se hace **necesario demostrar** que la invención analizada carece de nivel inventivo y hubiese sido obvia para una persona versada en la materia.

De acuerdo con lo anterior, y como se indicó en el numeral 3 del presente memorial, el solicitante escogió las reivindicaciones del **Grupo Inventivo 1** referido en el Oficio que se contesta para continuar con el proceso de patentabilidad de la presente solicitud. Adicionalmente, desea indicar que teniendo en cuenta las modificaciones presentadas en el nuevo capítulo reivindicatorio, se superan las objeciones realizadas, por cuanto **dichas características no se encuentran divulgadas en los documentos citados por el examinador.**

El examinador afirma que D2¹ divulga la administración de un inhibidor PARP y acetato de abiraterona en el tratamiento del cáncer de próstata resistente a la castración (mCRPC). El examinador reconoce que D2 no divulga el inhibidor de PARP que se reivindica actualmente (niraparib). En un intento de subsanar esta deficiencia, el examinador cita D3, que supuestamente describe la administración de niraparib a pacientes con mCPRC. Según el examinador, un experto en la materia estaría motivado para modificar la composición de D2 para incluir niraparib.

El examinador, sin embargo, no ha identificado ninguna razón por la que una persona con conocimientos ordinarios habría estado motivada para hacer esta modificación. De hecho, hay buenas razones para creer que dicha persona **no** habría estado motivada para modificar la enseñanza de D2 de la manera en la que el examinador propone.

Los expertos en la materia, por ejemplo, entendieron que no había razón para administrar veliparib con acetato de abiraterona porque hacerlo produce resultados que no son mejores que administrar acetato de abiraterona sin ningún veliparib. Este entendimiento se evidencia, por ejemplo, en una publicación de Hussain, *et al.* que informa sobre los resultados del documento D2 (Documento que se presenta como anexo a este memorial)². Hussain señala que “[a] pesar de las sólidas pruebas preclínicas de apoyo, **la adición de veliparib** a [acetato de abiraterona + prednisona] **no afectó a la respuesta**” (Hussain en la página 996, énfasis añadido). Como concluyó Hussain sucintamente, “[v]eliparib ... no afectó a la respuesta” (id. en 991)³.

Dada la demostración de Hussain en relación a que la combinación de veliparib, acetato de abiraterona y prednisona no era más eficaz que el acetato de abiraterona y la prednisona por sí solos, las personas con conocimientos ordinarios en la materia no

¹ Estudio NCT01576172 titulado “Abiraterone Acetate and Prednisone With or Without Veliparib in Treating Patients With Metastatic Castration-Resistant Prostate Cancer.”. El solicitante cree que el examinador incluyó por error el título de un estudio diferente (NCT01972217) en relación con esta referencia.

² Hussain, *et al.*, “Targeting Androgen Receptor and DNA Repair in Metastatic Castrations-Resistant Prostate Cancer: Results from NCI 9012,” *J Clin. Oncol.*, 36(10):991 (2018).

³ Una publicación reciente caracterizó el ensayo de manera similar:

Los pacientes fueron asignados aleatoriamente a recibir abiraterona (brazo A) o abiraterona con veliparib (300 mg dos veces al día, brazo B). **No hubo diferencias estadísticamente significativas entre los dos brazos en cuanto a la respuesta al [antígeno específico de la próstata]** (brazo A: 63,9% y brazo B: 72,4%, $p = 0,27$) **o la mediana de [supervivencia libre de progresión]** (brazo A: 10,1 meses y brazo B: 11 meses, $p = 0,99$). Hasta la fecha, no hay ningún otro ensayo en curso que investigue el veliparib en el cáncer de próstata.

Teyssonneau, *et al.*, *Journal of Hematology & Oncology*, 14:51 (2021) en la página 12 (énfasis añadido) (se adjunta copia a este memorial)

habrían tenido motivación para emplear esa combinación (en lugar de sólo abiraterona y prednisona), y ciertamente no habrían tenido ninguna motivación para emplear otra combinación en la que el inhibidor de PARP veliparib hubiera sido sustituido por otro inhibidor PARP como el niraparib. De hecho, a menos que una persona con conocimientos ordinarios ya conociera las invenciones reclamadas en la presente solicitud, habría creído que esas otras combinaciones que contienen PARP no mostraría ningún beneficio que no pudiera lograrse con el acetato de abiraterona y la prednisona solos.

D3 no se opone a la enseñanza combinada de D2 y Hussain, ni se afirma que lo haga. Se ha afirmado que D3 es relevante por su enseñanza de la administración de niraparib a pacientes con mCRPC. No hay ninguna razón para creer que esta enseñanaza habría llevado a aquellos con conocimientos ordinarios a administrar otro ingrediente activo con acetato de abiraterona, y mucho menos a administrar niraparib.

Además, la combinación reclamada de niraparib con acetato de abiraterona puede proporcionar una opción terapéutica en pacientes refractarios a las terapias existentes mediante un efecto terapéutico mejorado. Esto se confirma con el experimento *in vivo* descrito en el Ejemplo 2 de la solicitud, que proporciona la primera prueba de concepto para el tratamiento del cáncer de próstata con una combinación de inhibidores PARP e inhibidores de la biosíntesis de andrógenos. En este experimento, los ratones fueron inyectados por vía subcutánea con células de cáncer de próstata (VCaP), castrados, y luego dosificados en cuatro grupos: 1) vehículo de control; 2) niraparib; 3) abiraterona; y 4) niraparib y abiraterona. Se evaluó el crecimiento tumoral y la supervivencia de cada grupo. La combinación de abiraterona y niraparib proporcionó mejoras significativas en la inhibición del crecimiento tumoral (Figura 1) y la supervivencia (Figura 2) en comparación con la abiraterona o el niraparib por separado. Los datos de los Ejemplos de la presente descripción demuestran resultados sorprendentes e inesperados. La Tabla 4 proporciona datos que muestran el efecto de niraparib y/o acetato de abiraterona en la supervivencia de ratones portadores de tumores. La combinación de niraparib y acetato de abiraterona fue capaz de aumentar la vida de los ratones en un 31%. Este efecto no sólo es estadísticamente significativo (valor p de $<0,0001$), sino que es sorprendente porque el aumento observado en la duración de la vida es más que la adición de niraparib (-0,6%) y acetato de abiraterona (13,1%). Estos datos de supervivencia son sorprendentes e inesperados, sobre todo si se tiene en cuenta que no se observó ningún efecto cuando se añadió veliparib al acetato de abiraterona más prednisona en D2.

En resumen, las referencias citadas en la Acción Oficial que se contesta, tomadas solas o en conjunto, no enseñan ni sugieren ninguna combinación de acetato de abiraterona y niraparib.

De esta forma, teniendo en cuenta que los documentos D2 y D3, así como los documentos que se anexan, **no mencionan, describen o sugieren**, en forma individual o en combinación, todas las características técnicas reclamadas en el nuevo capítulo reivindicatorio presentado por el solicitante, **las nuevas reivindicaciones presentadas son novedosas, e inventivas sobre el estado del arte**.

En este sentido, y siguiendo el Manual Andino de Patentes, la presente invención tal y como se encuentra definida en las reivindicaciones 1 a 8, tiene diferencias con el estado del arte e implicó un nivel inventivo durante su desarrollo, por lo cual debe ser considerada como novedosa e inventiva según las disposiciones de los artículos 16 y 18 de la Decisión 486.

5. Conclusión

Con las modificaciones introducidas y los argumentos presentados puede concluirse que:

- i) La presente solicitud es clara, concisa y está debidamente soportada en la descripción, cumpliendo con los requerimientos del Artículo 30 de la Decisión 486;
- ii) Las reivindicaciones actuales presentan unidad de invención, cumpliendo así con los requerimientos del Artículo 25 de la Decisión 486; y
- iii) Las reivindicaciones actuales son patentables sobre D2 y D3, cumpliendo así con los requerimientos del Artículo 18 de la Decisión 486.

Por tanto, atentamente me permito solicitar a ese Despacho otorgar el privilegio de patente solicitado a la solicitud en estudio, toda vez que cumple a cabalidad con los requerimientos de la Decisión 486/00.

En consecuencia, solicitamos a ese Despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional.

6. Anexos

- Nuevo capítulo reivindicatorio conformado por 8 reivindicaciones.
- Recibo de pago correspondiente a Tasa de modificación a las reivindicaciones.
- Hussain, *et al.*, "Targeting Androgen Receptor and DNA Repair in Metastatic Castrations-Resistant Prostate Cancer: Results from NCI 9012," *J Clin. Oncol.*, 36(10):991 (2018).
- Teyssonneau, *et al.*, *Journal of Hematology & Oncology*, 14:51 (2021)

Señora Directora,



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REIVINDICACIONES MODIFICADAS

1. Una composición farmacéutica que comprende niraparib y acetato de abiraterona.
2. Las composiciones farmacéuticas según la reivindicación 1, donde la composición farmacéutica se constituye para administración oral.
3. Composición farmacéutica según la reivindicación 1 o la reivindicación 2, donde la composición farmacéutica comprende de 50 a 350 mg de niraparib y de 100 a 1500 mg de acetato de abiraterona.
4. Las composiciones farmacéuticas según la reivindicación 1 o la reivindicación 2, donde la composición farmacéutica comprende 50 mg de niraparib y 500 mg de acetato de abiraterona.
5. Las composiciones farmacéuticas según la reivindicación 1 o la reivindicación 2, donde la composición farmacéutica comprende 100 mg de niraparib y 500 mg de acetato de abiraterona.
6. La composición farmacéutica según una de las reivindicaciones anteriores, donde la composición comprende además prednisona o prednisolona.
7. La composición farmacéutica según la reivindicación 6, donde la composición comprende de 2 a 15 mg de prednisona o prednisolona.
8. La composición farmacéutica según la reivindicación 6 o 7, donde la composición comprende 5 mg de prednisona o prednisolona.

Targeting Androgen Receptor and DNA Repair in Metastatic Castration-Resistant Prostate Cancer: Results From NCI 9012

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Published at jco.org on December 20, 2017.

Clinical trial information: NCT01576172.

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0732-183X/18/3610w-991w/\$20.00

ABSTRACT

Purpose

To determine whether cotargeting poly (ADP-ribose) polymerase-1 plus androgen receptor is superior to androgen receptor inhibition in metastatic castration-resistant prostate cancer (mCRPC) and whether ETS fusions predict response.

Patients and Methods

Patients underwent metastatic site biopsy and were stratified by ETS status and randomly assigned to abiraterone plus prednisone without (arm A) or with veliparib (arm B). Primary objectives were: confirmed prostate-specific antigen (PSA) response rate (RR) and whether ETS fusions predicted response. Secondary objectives were: safety, measurable disease RR (mRR), progression-free survival (PFS), and molecular biomarker analysis. A total of 148 patients were randomly assigned to detect a 20% PSA RR improvement.

Results

A total of 148 patients with mCRPC were randomly assigned: arm A, $n = 72$; arm B, $n = 76$. There were no differences in PSA RR (63.9% v 72.4%; $P = .27$), mRR (45.0% v 52.2%; $P = .51$), or median PFS (10.1 v 11 months; $P = .99$). ETS fusions did not predict response. Exploratory analysis of tumor sequencing (80 patients) revealed: 41 patients (51%) were ETS positive, 20 (25%) had DNA-damage repair defect (DRD), 41 (51%) had *AR* amplification or copy gain, 34 (43%) had *PTEN* mutation, 33 (41%) had *TP53* mutation, 39 (49%) had PIK3CA pathway activation, and 12 (15%) had WNT pathway alteration. Patients with DRD had significantly higher PSA RR (90% v 56.7%; $P = .007$) and mRR (87.5% v 38.6%; $P = .001$), PSA decline $\geq 90\%$ (75% v 25%; $P = .001$), and longer median PFS (14.5 v 8.1 months; $P = .025$) versus those with wild-type tumors. Median PFS was longer in patients with normal *PTEN* (13.5 v 6.7 months; $P = .02$), *TP53* (13.5 v 7.7 months; $P = .01$), and PIK3CA (13.8 v 8.3 months; $P = .03$) versus those with mutation or activation. In multivariable analysis adjusting for clinical covariates, DRD association with PFS remained significant.

Conclusion

Veliparib and ETS status did not affect response. Exploratory analysis identified a novel DRD association with mCRPC outcomes.

J Clin Oncol 36:991-999. © 2017 by American Society of Clinical Oncology

INTRODUCTION

Despite a high response rate (RR) to androgen deprivation (AD), a majority of patients with metastatic prostate cancer (PCa) will experience progression to castration resistance. Advances in understanding the biology and progression mechanisms to castration resistance led to development and approval of novel androgen receptor (AR)–targeted therapies: abiraterone acetate plus

prednisone (AAP) and enzalutamide.^{1,2} Both prolong survival in metastatic castration-resistant prostate cancer (mCRPC) irrespective of prior docetaxel.^{3,4} However, many patients exhibit de novo resistance to both therapies, and resistance invariably occurs in responders, warranting a search for better treatments.⁵⁻⁸

Several studies have shown that AR regulates components of DNA-repair pathways, and conversely, several enzymes involved in DNA repair can modulate AR activity.⁹⁻¹⁵ An important example is

ASSOCIATED CONTENT



See accompanying article on page 1017



Appendix
DOI: <https://doi.org/10.1200/JCO.2017.75.7310>

DOI: <https://doi.org/10.1200/JCO.2017.75.7310>

poly (ADP-ribose) polymerase-1 (PARP1), an enzyme with essential roles in recognition and repair of single-strand DNA breaks through base excision repair process.¹⁶ Several cancers, including CRPC, exhibit increased PARP1 expression and/or activity.¹⁶⁻¹⁹ Compelling data implicate PARP1 in mediation of DNA-repair responses to alkylators, cellular survival in BRCA-deficient cells, and AR-mediated PCa cell proliferation.^{16,20-23} Specifically, preclinical studies using PARP1 inhibitors (eg, veliparib, olaparib) in PCa showed that PARP1 activity was required for maximal AR function.¹⁶ In vivo, PARP1 inhibition with veliparib was as effective as castration in preventing tumor growth, and even greater inhibition was achieved with combination veliparib and castration.¹⁶

Canonic ETS gene fusions (androgen-responsive promoters driving ETS transcription factor overexpression) are present in > 50% of patients with PCa. ERG, the predominant ETS gene fusion product, physically interacts with PARP1.²⁴⁻²⁶ PARP1 is required for full ERG activity and its downstream oncogenic functions. ERG-positive xenografts are preferentially sensitive to PARP1 inhibitors.²⁶

On the basis of these data, we hypothesized that in patients with mCRPC, cotargeting AR and PARP1 would result in a better RR than AAP and the combination would be most effective in patients with ETS fusion-positive tumors.

PATIENTS AND METHODS

Patients

Eligible patients had mCRPC, Eastern Cooperative Oncology Group performance status of 0 to 2, testosterone < 50 ng/dL, normal organ function, no prior exposure to AAP, and up to two prior chemotherapy regimens. Complete eligibility criteria are outlined in the Study Protocol. All patients provided written informed consent per institutional and federal guidelines.

Study Design, Treatment, and End Points

This was a biomarker-stratified and randomized phase II multicenter trial (Fig 1). The primary objectives were to evaluate whether AAP plus veliparib is superior to AAP, as reflected by prostate-specific antigen (PSA)

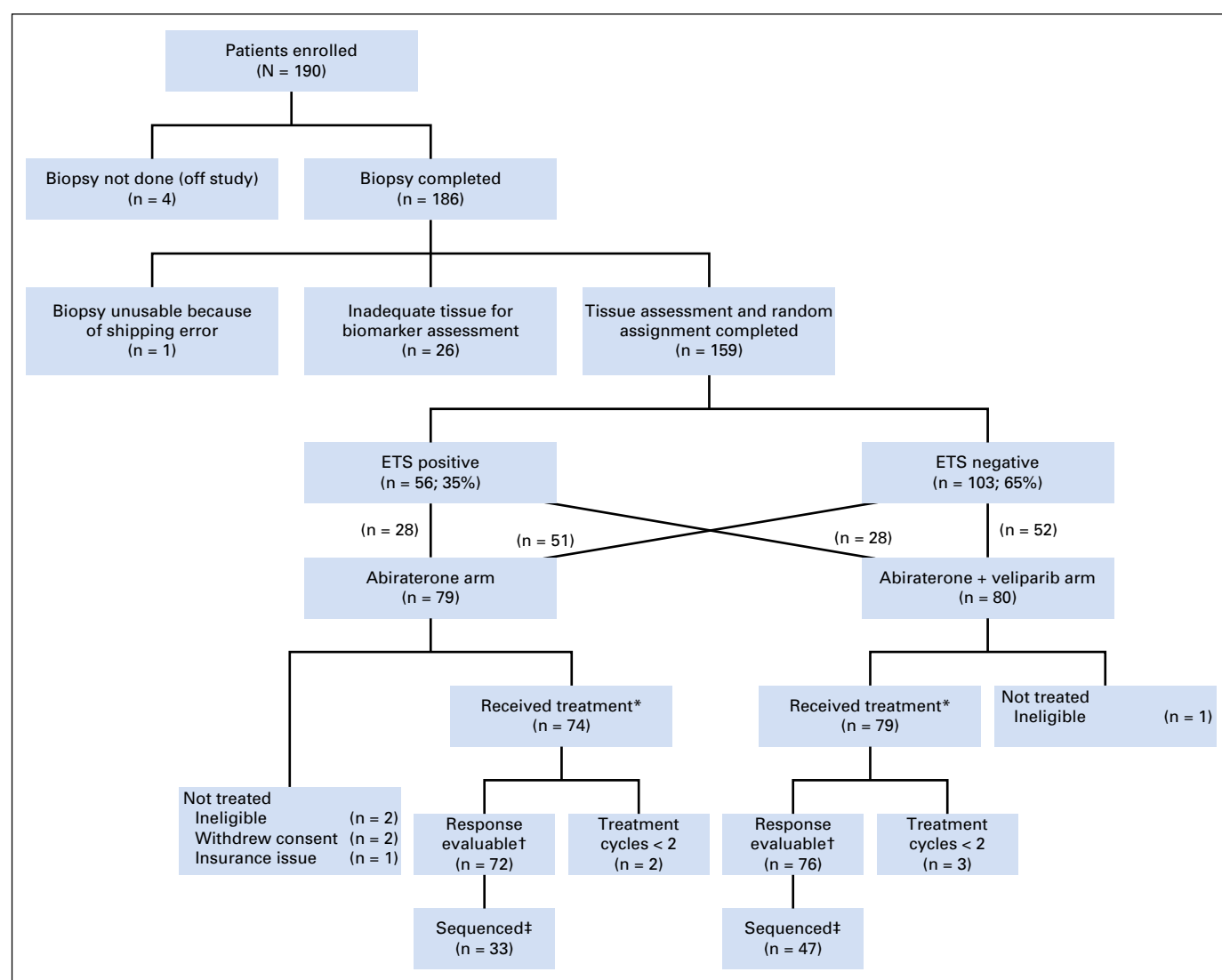


Fig 1. CONSORT diagram. (*) Safety evaluable. (†) Defined as having received two cycles of therapy or removed because of toxicity; five patients who received < two cycles did so by patient choice. (‡) Sequencing completed for all patients with sufficient extra tissue from biopsy required for sequencing.

RR ($\geq 50\%$ decline), and whether ETS gene fusion predicts response. Other end points included measurable disease RR (mRR), progression-free survival (PFS), toxicities, and exploratory tumor molecular analysis.

All patients underwent metastatic disease biopsy (unless metastatic archival tissue was available). ETS status was determined by immunohistochemistry (IHC) for ERG and in situ hybridization (ISH)–based assays for ETV1 fusions,^{27,28} conducted in a College of American Pathologists/Clinical Laboratory Improvement Amendments–accredited laboratory. The study was activated before AAP approval in prechemotherapy setting. Eligible patients were stratified by prior ketoconazole and ETS fusion status (positive or negative) and randomly assigned to AA 1,000 mg per day plus prednisone 5 mg twice per day (arm A) or AAP plus veliparib 300 mg twice per day (arm B), for days 1 to 28. Arm B patients underwent lead-in treatment with AAP, followed on day 8 by veliparib, in cycle 1 only. Treatment was continued until radiographic/clinical disease progression, intercurrent illness, unacceptable adverse events (AEs), withdrawal of consent, or death.

Assessments

Patients underwent baseline disease assessments and then every 12 weeks with bone scan, computed tomography or magnetic resonance imaging of abdomen/pelvis, and x-ray or computed tomography of chest for the first year. For patients who have completed ≥ 1 year of therapy, imaging can be done every 4 months, and for patients who have completed ≥ 2 years of therapy, imaging can be done every 6 months. Irrespective of duration on therapy, imaging can be done sooner than the specified intervals as clinically indicated. PSA was assessed at baseline and on day 1 of each cycle. AEs were graded according to Common Terminology Criteria for Adverse Events (version 4.0).

Tumor Sequencing

Extra tumor tissue for sequencing was available for 87 patients; 80 of 87 were response evaluable (four patients received < 2 cycles of treatment, three patients were never treated, one was ineligible, and two withdrew consent). Their baseline characteristics are detailed in Appendix Tables A1 and A2 (online only). Flash-frozen biopsies were processed for genomic DNA and total RNA isolation using Qiagen AllPrep Kit (Hilden, Germany) and then underwent targeted exon sequencing and capture transcriptome analysis at University of Michigan (Ann Arbor, MI), as previously detailed.^{29,30}

Statistical Analysis

Biomarker-stratified design³¹ was used to determine a PSA RR difference between arms A and B and between arms by ETS fusion (positive v negative strata). The trial was designed to accrue 148 response-evaluable patients randomly assigned at a one-to-one ratio to arms A and B to provide 80% power at a one-sided 5% significance level to detect an improvement of 20% in PSA RR between arms with a χ^2 test of proportions, assuming a PSA RR of 30% in arm A (based on data available at time of study design).¹ Response-evaluable patients were those receiving at least two therapy cycles or those removed from study because of toxicity before completing two cycles. The PSA RR difference between treatment groups by ETS fusion status was an interaction test with a significance threshold of .15 from a logistic model (trial design details provided in protocol).

The primary outcome of confirmed PSA RR (complete or partial response) was analyzed with χ^2 tests to test differences between treatment arms and differences within a biomarker stratum between treatment arms. Confirmed PSA RR was modeled to test ETS fusion status as prognostic using a logistic model with ETS status as the only covariate and as predictive using logistic models testing interaction of treatment arm and ETS. Similar models were used for mRR. Both prognostic and predictive models were used in the exploratory analyses for each sequencing biomarker including DNA-damage repair defect (DRD). Secondary end point PFS was reported using Kaplan-Meier methods and associated log-rank tests.

Exploratory analysis for prognostic biomarkers with association with PFS was reported using product-limit estimates and log-rank tests. Cox models were used to test biomarkers as predictive of PFS with models including an interaction of treatment arm and biomarker status. An unplanned analysis using a multivariable Cox model for PFS was used to explore biomarker associations with PFS after controlling for clinical covariates by adding the biomarker to the model including the clinical covariates. Each biomarker was modeled separately. All analyses were completed using SAS software (version 9.4; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

From May 2012 through December 2015, 190 patients with mCRPC were enrolled at 12 centers (Table 1); 185 eligible patients underwent metastatic biopsy (soft tissue, n = 89; bone, n = 96); 159

Table 1. Baseline Patient Demographic and Clinical Characteristics by Treatment Arm

Characteristic	No. (%)		P
	Arm A: Abiraterone (n = 74)	Arm B: Abiraterone + Veliparib (n = 79)	
Age, years			.35
Median	69	68	
Range	50-90	47-85	
Race			.09
White	61 (82.4)	74 (93.7)	
Black	9 (12.2)	3 (3.8)	
Other	4 (3.4)	2 (2.5)	
Performance status			.93
0	46 (62.2)	50 (63.3)	
1	28 (37.8)	28 (35.4)	
2	0	1 (1.3)	
PSA, ng/mL			.67
Median	32.7	36.4	
Range	0.8-1,557.6	0.04-1,074.4	
Cancer pain present	23 (31.1)	26 (33.0)	.81
Sites of disease			
Bone	64 (86.5)	68 (86.1)	.94
Lymph node	45 (60.8)	53 (67.1)	.42
Visceral	13 (17.6)	21 (26.6)	.18
Other	13 (17.6)	16 (20.3)	.67
Previous treatments			
Chemotherapy	16 (20.8)	23 (30.3)	.29
Docetaxel/cabazitaxel	11 (14.9)	17 (21.5)	
Other	5 (6.8)	6 (7.6)	
Enzalutamide	2 (2.7)	2 (2.5)	.99
Sipuleucel-T	22 (29.7)	13 (16.5)	.05
Experimental agent	19 (25.7)	15 (19.0)	.32
Strata: ETS fusion and ketoconazole use			.83
ETS fusion positive*	25 (33.8)	28 (35.4)	
ETS fusion negative	49 (66.2)	51 (64.6)	
Previous ketoconazole	8 (10.8)	9 (11.3)	.91
No. of treatment cycles			.68
Median	9	9	
Range	1-46	1-50	
Overall survival			—
Median	30.6	32.3	
95% CI	28.4 to NR	28.4 to NR	

Abbreviations: NR, not reached; PSA, prostate-specific antigen.

*ETS fusion determined by immunohistochemistry/in situ hybridization.

patients (86%) had adequate tissue; 35% were ETS positive; 153 patients (white, 88%; black, 8%; median age, 68 years; median PSA, 35.4 ng/mL) were randomly assigned to arm A (AAP; n = 74) or arm B (AAP + veliparib; n = 79; Fig 1).

Safety

Because of bothersome low-grade AEs, veliparib dose was reduced to 200 mg twice per day for cycle 1, and if tolerated, dose was escalated to 300 mg twice per day for subsequent cycles. Distribution of grade ≥ 3 AEs irrespective of attribution was similar between arms. Overall, therapy was well tolerated (Appendix Table A3, online only); hyperglycemia was the only high-grade treatment-related AE that occurred in $> 5\%$ of patients in either arm (arm A, 9%; arm B, 5%). In arm A, 20% of patients (n = 15) had grade 3 treatment-related AEs, and one patient had grade 4 hyperglycemia. In arm B, 24% of patients (n = 19) had grade 3 treatment-related AEs, one patient had grade 4 thrombocytopenia, and one patient had grade 5 cardiac arrest possibly treatment related. Any-grade AEs that were significantly more frequent ($P < .05$) in arm B versus arm A were fatigue, lymphopenia, nausea, and vomiting; edema occurred more frequently in arm A than arm B.

Efficacy

Of the 153 randomly assigned and treated patients, 148 were response evaluable; five (3%) were not evaluable (four patients chose to stop treatment within one cycle, and one had > 4 -week treatment delay). There was no statistically significant difference between arms in confirmed PSA RR (arm A, 63.9%; arm B, 72.4%; $P = .27$), mRR (arm A, 45.0%; arm B, 52.2%; $P = .51$), or median PFS (arm A, 10.1 months; arm B, 11 months; $P = .99$; Table 2; Appendix Fig A1A). Furthermore, ETS fusion status did not predict PSA, mRR, or PFS (Appendix Fig A1B).

DRD and Additional Prognostic Biomarkers

For 87 patients, extra biopsy tumor tissue was analyzed by next-generation sequencing; 80 of 87 were treated and response evaluable (arm A, n = 33; arm B, n = 47). Sequenced patients' characteristics compared with those of patients who did not have tumor sequencing and their baseline characteristics by treatment arm are listed in Appendix Tables A1 and A2. Overall, the groups were fairly comparable, except for site of disease (bone v soft tissue [eg, lymph node, visceral disease]), which affected the site of biopsy: in the sequenced cohort, a majority (75%) were soft tissue biopsies, whereas in the nonsequenced population, a majority (70%) had bone biopsies. This is not surprising, considering tumor yield is known to be better with soft tissue biopsy. The tumor yield likely affected the difference between the two groups in the proportion of patients with ETS-positive tumors, which was higher in the sequenced group.

ETS fusion status was also analyzed by sequencing to evaluate concordance with the IHC/ISH methods used. Agreement between methods was observed for 72 (90%) of 80 patients (Appendix Table A4, online only); 41 patients (51.3%) were ETS positive by sequencing.

Sequencing classified patients into three categories of DNA-repair status (Fig 2A): wild type (WT; n = 55 [68.75%]), biallelic DRD (n = 20 [25%]), and monoallelic DRD (n = 5 [6.25%]). Patients with DRD had alterations in *BRCA1*, *BRCA2*, *ATM*, *FANCA*, *PALB2*, *RAD51B*, or *RAD51C*, with *BRCA2* being the most frequently detected (Fig 2A). Notably, these genes represent major players in the homologous recombination (HR) pathway, which functions along with the nonhomologous end-joining (NHEJ) pathway to repair DNA double-strand breaks.¹⁵ Additional genes of interest were also significantly altered, including *AR* (n = 41 [51%]), *TP53* (n = 33 [41%]), *PTEN* (n = 34 [42.5%]), and *PIK3CA* (n = 39 [49%]). Alterations were also annotated for AR-related genes and the WNT pathway.

Table 2. Detailed PSA and Measurable Response Outcomes by Treatment Arm and ETS Gene Fusion Status

Response	Overall (n = 148)			ETS Positive (n = 52)			ETS Negative (n = 96)			Interaction <i>P</i>
	No. (%)			No. (%)			No. (%)			
	Abiraterone	Abiraterone + Veliparib	<i>P</i>	Abiraterone	Abiraterone + Veliparib	<i>P</i>	Abiraterone	Abiraterone + Veliparib	<i>P</i>	
PSA outcomes	(n = 72)	(n = 76)		(n = 25)	(n = 27)		(n = 47)	(n = 49)		
PSA response (CR/ PR)	46 (63.9)	55 (72.4)	.27	15 (60.0)	19 (70.4)	.43	31 (66.0)	36 (73.5)	.42	.89
CR	12 (16.7)	12 (15.8)		4 (16.0)	3 (11.1)		8 (17.0)	9 (18.4)		
PR	34 (47.2)	43 (56.6)		11 (44.0)	16 (59.3)		23 (48.9)	27 (55.1)		
Stable disease	19 (26.4)	15 (19.7)		7 (28.0)	7 (25.9)		12 (25.5)	8 (16.3)		
Progressive disease	7 (9.7)	6 (7.9)		3 (12.0)	1 (3.7)		4 (8.5)	5 (10.2)		
Measurable disease	(n = 40)	(n = 46)		(n = 15)	(n = 19)		(n = 25)	(n = 27)		
RECIST response (CR/PR)	18 (45.0)	24 (52.2)	.51	6 (40.0)	10 (52.6)	.46	12 (48.0)	14 (51.9)	.78	.69
CR	1 (2.5)	0 (0)		0 (0)	0 (0)		1 (4.0)	0 (0)		
PR	17 (42.5)	24 (52.2)		6 (40.0)	10 (52.6)		11 (44.0)	14 (51.9)		
Stable disease	14 (35.0)	12 (26.1)		5 (33.3)	6 (31.6)		9 (36.0)	6 (22.2)		
Progressive disease	8 (20.0)	8 (17.4)		4 (26.7)	3 (15.8)		4 (16.0)	5 (18.5)		
Not evaluable	0 (0)	2 (4.4)		0 (0)	0 (0)		0 (0)	2 (7.4)		

Abbreviations: CR, complete response; PR, partial response; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors.

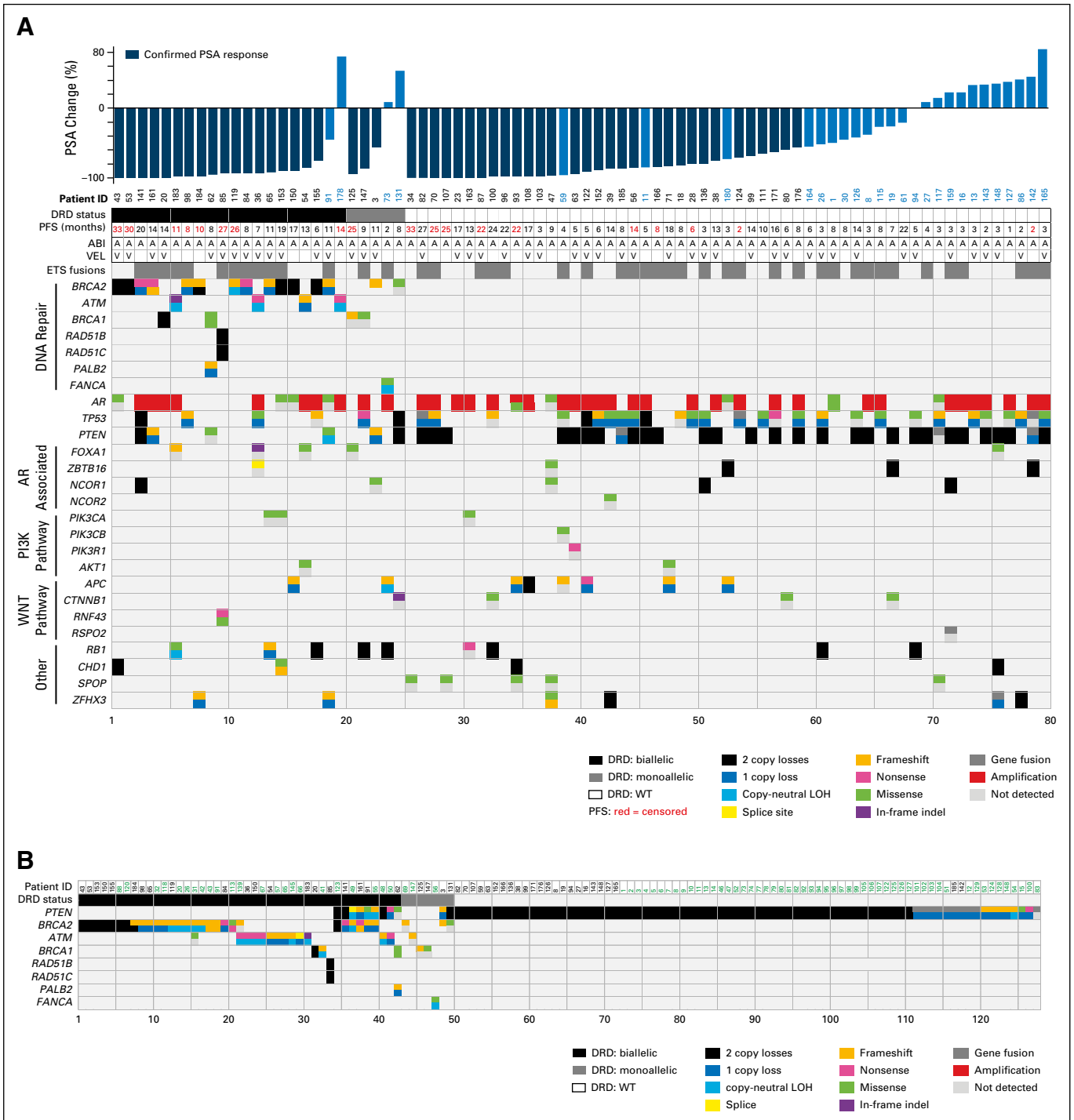


Fig 2. Landscape of molecular alterations, DNA-repair status, and survival in this cohort of patients with metastatic castration-resistant prostate cancer (mCRPC). (A) Next-generation sequencing of tumor tissues identified alterations in different genes for each patient (n = 80) as depicted in the matrix, called by each allele. Three groups of patients were determined based on DNA-damage repair defect (DRD) status, represented at the top by black (biallelic DRD), gray (monoallelic DRD), or white boxes (wild-type [WT] DRD). Above this, maximum percent decreases in prostate-specific antigen (PSA) levels throughout treatment are graphed for each patient, and those with confirmed PSA responses are noted with dark blue bars. Progression-free survival (PFS; months), treatment (abiraterone [A/ABI], veliparib [V/VEL]), and ETS fusion status are also indicated at the top of the matrix for each patient. (B) Matrix of DRD status associated with *PTEN* alterations. Patients along the top in black correspond to patients in this study, and patients in green represent cases from an additional mCRPC cohort.²⁹ (C) PFS curves are shown for patients with WT/monoallelic or biallelic DRD status. LOH, loss of heterozygosity.

Outcome analysis combined WT and monoallelic DRD patients, because the DRD status of the latter group is considered nondeleterious, and compared them with biallelic DRD patients. Prognostic covariates

(metastatic site, performance status, PSA, pain, and prior therapies) were similar between DRD and WT groups except for prior sipuleucel-T therapy (DRD, n = 1 [5%] v WT, n = 16 [29%]).

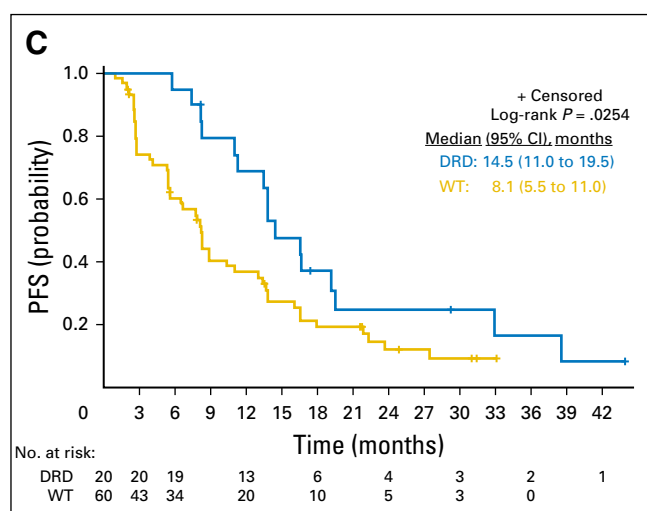


Fig 2. (Continued).

Unexpectedly, we uncovered a novel, significant association between DRD and overall outcome/response. Patients with DRD tumors had significantly higher confirmed PSA RR (90% *v* 56.7%; $P = .007$; Table 3; Fig 2A), PSA decline of $\geq 90\%$ (75% *v* 25%; $P = .001$; Appendix Fig A2, online only), mRR (87.5% *v* 38.6%; $P = .001$; Table 3), and median PFS (14.5 *v* 8.1 months; $P = .025$; Fig 2C; depicted by treatment arm in Fig 3) compared with patients with WT tumors.

Analysis of Clinical and Molecular Variables

Exploratory biomarker analysis revealed three additional biomarkers associated with longer median PFS (Appendix Tables A5 and A6, online only). Significantly better overall outcomes were identified in patients with normal *PTEN* (13.5 *v* 6.7 months in those with mutation; $P = .02$), normal *TP53* (13.5 *v* 7.7 months in those with mutation; $P = .01$), or nonactivated *PIK3CA* pathway (13.8 *v* 8.3 months in those with activation; $P = .03$; Appendix Table A5, online only). Multivariable analysis including clinical and biomarker variables individually revealed DRD and *TP53* as biomarkers separately associated with PFS after controlling for clinical covariates (Table 4). We also noted that mutation or loss of *PTEN* seemed to be almost mutually exclusive with DRD (Fig 2A).

Exceptional Responders

Several patients had exceptional and durable responses to therapy. These were patients in either arm with PFS > 24 months and PSA decline $> 90\%$. On the basis of these criteria, 19 exceptional responders (arm A, $n = 8$; arm B, $n = 11$) were identified; their characteristics are listed in Appendix Table A7 (online only). Nine of 19 had tumor sequencing: four had biallelic DRD, one had monoallelic DRD, and four had WT tumors (Fig 2A; Appendix Table A8, online only).

DISCUSSION

This prospective metastatic tissue-based biomarker-stratified trial stratified patients with mCRPC by ETS fusion status and then randomly assigned them to AAP with or without veliparib. Preclinical data suggested that targeting PARP1 would synergize with AR inhibition, and ETS fusion-positive tumors would be preferentially sensitive to PARP1 inhibition.^{13,16,26} However, the addition of veliparib did not affect response, nor did ETS status predict response. There was no difference between arms in the rate of exceptional responders (AAP, $n = 8$; AAP + veliparib, $n = 11$). ETS fusion concordance between IHC/ISH and sequencing was 90%. ERG/ETS failure to predict response may have been a result of the high prevalence of defects in DRD genes (approximately 25% of patients), which was not known at time of study design.

Exploratory metastatic tissue sequencing analysis uncovered a novel finding. Several patients had alterations in genes involved in DNA repair, particularly those implicated in the HR pathway; DRD was significantly associated with better response and PFS irrespective of treatment arm. Prior studies demonstrated mechanistic connections between AR and DNA repair in prostate cancer models,⁹⁻¹⁵ but ours is the first report, to our knowledge, to show the association of DRD with outcome in patients with mCRPC treated with AAP with higher PSA RR, mRR, and PFS compared with patients with WT tumors. However, additional studies are needed for confirmation, because this trial was not designed specifically to test DRD predictive power with AR-targeted therapy. A recent trial in mCRPC showed that DRD was associated with high RRs to a different PARP1 inhibitor (olaparib), but there was no control arm of an AR-targeted agent.³²

Table 3. PSA and Measurable Disease Response Rate by DNA Repair Status

TABLE 2. PSA and Measurable Disease Response Rate by DNA-Repair Status										
Response	Prognostic Biomarker			DRD (n = 20)			DNA-Repair WT/Monoallelic (n = 60)			Interaction <i>P</i>
	No. (%)		<i>P</i>	No. (%)		<i>P</i>	No. (%)		<i>P</i>	
	DRD	DNA-Repair WT/ Monoallelic		Abiraterone	Abiraterone + Veliparib		Abiraterone	Abiraterone + Veliparib		
PSA	(n = 20)	(n = 60)		(n = 7)	(n = 13)		(n = 26)	(n = 34)		
PSA response	18 (90.0)	34 (56.7)	.007	6 (85.7)	12 (92.3)	1.0	12 (46.2)	22 (64.7)	.15	.97
95% CI, %	76.9 to 100	44.1 to 69.2		59.8 to 100	77.8 to 100		27.0 to 65.3	48.6 to 80.8		
Measurable disease	(n = 16)	(n = 44)		(n = 5)	(n = 11)		(n = 19)	(n = 25)		
RECIST response	14 (87.5)	17 (38.6)	.001	4 (80.0)	10 (90.9)	1.0	7 (36.8)	10 (40.0)	.83	.64
95% CI, %	59.5 to 98.3	24.1 to 54.0		44.9 to 100	73.9 to 100		15.2 to 58.5	20.8 to 59.2		

Abbreviations: DRD, DNA-damage repair defect; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; WT, wild type.

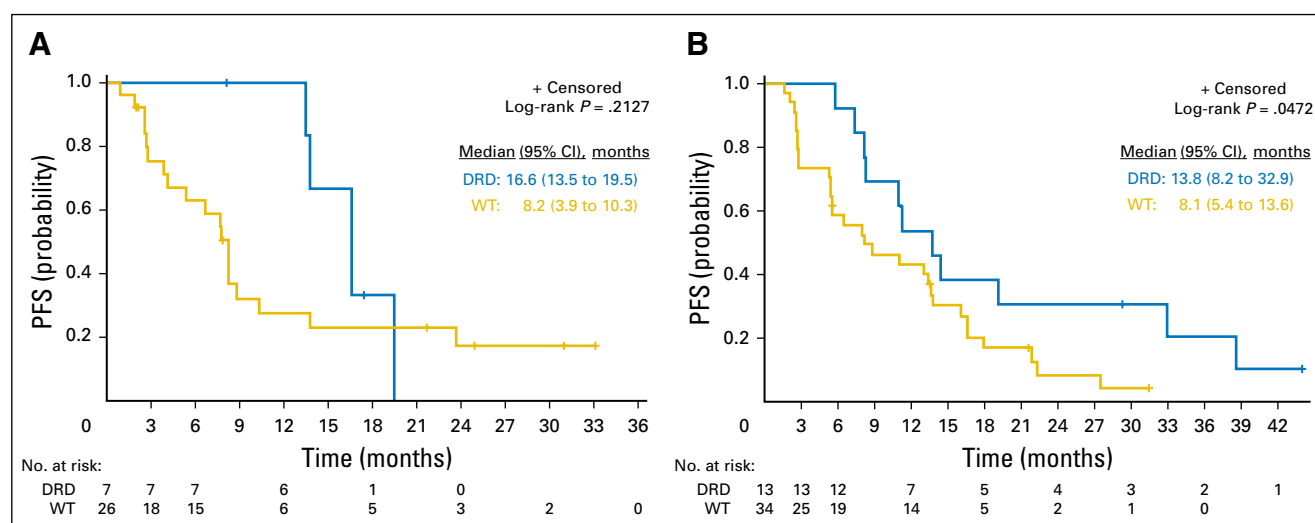


Fig 3. Survival by DNA-repair status and treatment arm. Progression-free survival (PFS) curves are shown by treatment arm for patients with wild-type (WT)/monoallelic or biallelic DNA-damage repair defect (DRD), as determined by next-generation sequencing of tumors shown in Figure 2 of the main manuscript: (A) abiraterone/prednisone; (B) abiraterone/prednisone plus veliparib.

AR plays a major role in promoting double-strand DNA break repair.^{12,13} As such, AR blockade alone would be expected to compromise DNA repair. This concept is supported by our data, wherein tumors defective in DNA repair were sensitized to AAP. Given this recently realized redundancy in function (eg, capacity of both PARP1 inhibitors and AR blockade to suppress DNA repair), it is not unexpected that PARP1 inhibitors did not add to AR blockade.

Our results also raise the question of how DNA repair alterations may be associated with better outcomes with AR-targeted therapy. Recent studies have shown that AR directly regulates genes involved in DNA-damage responses that allow prostate cancer cells to enhance DNA repair, decrease DNA damage, and continue cycling.^{10,12,13,15} Conversely, castration or treatment with anti-androgens leads to decreased expression of DNA-repair enzymes and therefore increased DNA damage and decreased cellular survival; in particular, inhibition of AR signaling has been shown to

inhibit the expression of genes primarily involved in the NHEJ pathway of double-strand DNA break repair.¹¹⁻¹⁴ Disruption of NHEJ in the context of an underlying HR defect (the alterations identified in this trial cohort) could induce a synthetic lethality via disruption of both of the major repair pathways for double-stranded DNA breaks, thus explaining why patients with HR deficiencies fare better with AAP treatment. Furthermore, as described in this report, AR directly increases DNA-damage response effectors, and in turn, many DNA-damage response proteins directly modulate AR activity, including BRCA1 and BRCA2, two HR factors altered in several of the DRD patients.^{33,34} Without functional BRCA1 or BRCA2 cofactors, it can be hypothesized that these patients may have had altered AR transcriptional activity compared with WT patients. Further analysis of the sequencing data herein uncovered a positive association with outcome for patients with normal expression of *PTEN* and *TP53* or nonactivated

Table 4. Multivariable Analysis of PFS by Biomarker Status (n = 80)

Biomarker	Marker Status					Cox Model	
	Not Normal		Normal		Log-Rank <i>P</i>	Univariable	Multivariable*
	No. (%)	Median PFS (months) (95% CI)	No. (%)	Median PFS (months) (95% CI)		Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
DRD v WT/monoallelic	20 (25)	14.5 (11.0 to 19.5)	55 (69)	8.0 (5.4 to 13.0)	.02	0.52 (0.29 to 0.93)	0.51 (0.27 to 0.97)
<i>TP53</i> (mutated v normal)	33 (41)	7.7 (5.3 to 8.8)	47 (59)	13.5 (8.2 to 16.6)	.01	1.88 (1.14 to 3.12)	2.52 (1.30 to 4.89)
<i>PTEN</i> (mutated v normal)	34 (43)	6.7 (4.1 to 11.3)	46 (57)	13.5 (8.2 to 16.6)	.02	1.82 (1.11 to 3.01)	1.61 (0.92 to 2.82)
<i>PIK3CA</i> (activated v normal)	39 (49)	8.3 (5.4 to 13.3)	41 (51)	13.8 (8.2 to 16.6)	.03	1.74 (1.05 to 2.87)	1.45 (0.79 to 2.68)
<i>SPOP</i> (mutated v normal)	5 (6)	NR (2.8 to NR)	75 (94)	8.8 (7.8 to 13.6)	.06	0.28 (0.07 to 1.15)	0.54 (0.09 to 3.40)
<i>CHD1</i> (mutated v normal)	4 (5)	NR (2.6 to NR)	76 (95)	8.8 (7.8 to 13.6)	.09	0.31 (0.07 to 1.29)	0.39 (0.09 to 1.71)
<i>AR</i> (amplified/mutated v normal)	41 (51)	8.8 (5.4 to 13.5)	39 (49)	11.0 (8.0 to 16.6)	.17	1.41 (0.86 to 2.31)	1.34 (0.80 to 2.23)
<i>ZFX3</i> (mutated v normal)	6 (8)	10.0 (2.1 to 13.8)	74 (92)	10.3 (8.0 to 13.8)	.20	1.74 (0.74 to 4.09)	1.44 (0.57 to 3.63)
<i>RB1</i> (mutated v normal)	9 (11)	8.8 (1.9 to 23.7)	71 (89)	10.3 (8.0 to 13.8)	.46	1.32 (0.62 to 2.78)	1.47 (0.66 to 3.28)
ETS (positive v negative)	41 (51)	8.2 (5.4 to 14.5)	39 (49)	13.3 (8.2 to 13.8)	.48	1.19 (0.73 to 1.95)	1.24 (0.45 to 3.38)
WNT (activated v normal)	12 (15)	12.4 (2.7 to 23.7)	68 (85)	10.3 (8.0 to 13.6)	.91	0.96 (0.5 to 1.85)	0.88 (0.44 to 1.74)

Abbreviations: DRD, DNA-damage repair defect; NR, not reached; PFS, progression-free survival; WT, wild type.

*Multivariable model includes age, baseline prostate-specific antigen, race, Eastern Cooperative Oncology Group performance status, treatment arm, prior chemotherapy, prior ketoconazole, fusion status stratum, and biomarker of interest.

PIK3CA pathway. However, multivariable analysis including clinical and biomarker variables individually revealed DRD and TP53 as biomarkers separately associated with PFS after controlling for clinical covariates. Expanded analysis of DRD and *PTEN* from an additional mCRPC cohort²⁹ demonstrated that DRD patients had significantly less aberrations in *PTEN*, whereas patients with WT DNA repair all had *PTEN* loss or aberration. The mutual exclusivity between DRD and *PTEN* could further explain why patients with WT DNA repair had worse outcome with therapy. *PTEN* loss has been associated with more aggressive prostate cancers, and pre-clinical models have suggested that *PTEN* loss/PIK3CA pathway activation can alter AR transcriptional activity and lead to hormonal therapy resistance.^{35,36} Directly related to our results, in retrospective analyses of patients with mCRPC receiving AAP in the postdocetaxel setting, *PTEN* loss was associated with shorter overall survival from time of initiation of AAP treatment.³⁷

In contrast to findings presented here, a recent study proposed that patients with germline DRD have decreased time from androgen-deprivation therapy initiation to castration resistance and worse outcome with first-line hormonal therapy once CRPC develops.³⁸ Important differences in these two studies are evident and could account for discrepancies. In our trial, DRD was determined by metastatic tumor tissue sequencing, the gold standard for detecting alterations. The contrasting study did not analyze tumor tissue but rather defined DRD through targeted germline sequencing. The WT DNA repair patients with whom the DRD patients were compared were only classified as such through germline sequencing, thus not accounting for those WT germline patients who may have acquired somatic DRD events. Indeed, the authors proceeded to sequence cell-free DNA, but only from those patients who were first determined to have germline DRD; these patients totaled 21 in comparison with the 80 tumors sequenced in our study. Finally, the patients with mCRPC in the previous study were treated with enzalutamide or AAP; in contrast, patients in our trial all received AAP.

There are several limitations in our study. The analyses of the biomarkers from sequencing were unplanned and exploratory and included a convenient sample of 80 of 148 patients who had extra biopsy tissue. The sequenced cohort included more soft tissue biopsies compared with patients who were not sequenced. This is not surprising, considering the known fact that the tissue yield is better from soft tissue metastases. The tumor tissue yield also likely affected the difference in the rate of ETS-positive tumors between the two cohorts. The multivariable modeling included many covariates for the sample size, so caution should be taken when interpreting these results. Additionally, there was not a correction

for multiple comparisons in this study. Additional validation is needed for the exploratory findings.

In conclusion, this metastatic tissue biomarker-stratified, randomized trial in mCRPC showed that the approach is feasible. Despite robust preclinical supporting evidence, the addition of veliparib to AAP did not affect response, nor did ETS fusion predict response. Nonetheless, exploratory analysis led to the novel and unexpected finding that DRD was associated with improved outcomes with AAP treatment, possibly through induction of a synthetic lethality in the context of HR defects. Interestingly, DRD was also generally associated with normal *PTEN* status. Normal *PTEN*, normal *TP53*, and nonactivated PIK3CA signaling were significantly associated with improved outcome overall. These hypothesis-generating observations are being evaluated in a follow-up DRD-preselected randomized trial (AAP v olaparib v combination). These results highlight the complexity of mCRPC, importance of the totality of the biologic context, and need for informative clinical trial designs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Supported by Grants No. N01-CM-2011-00071C from the National Cancer Institute (NCI), SU2C-AACR-DT0712 from Stand up to Cancer and American Association for Cancer Research, P50CA186786 from NCI, PC080189 from the US Department of Defense, and the Prostate Cancer Foundation.

Prior Presentation

Presented at the 52nd Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, IL, June 3-7, 2016, and 53rd ASCO Annual Meeting, Chicago, IL, June 2-6, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Targeting Androgen Receptor and DNA Repair in Metastatic Castration-Resistant Prostate Cancer: Results From NCI 9012

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifu.

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Acknowledgment

We thank Stephanie Ellison for assistance in formatting and writing this manuscript as well as the Mi-Oncoseq clinical sequencing laboratory for sequence analysis of samples in this study. We are especially grateful to all the patients who participated in this investigational study. We would also like to thank the Michigan Center for Translational Pathology.

Appendix

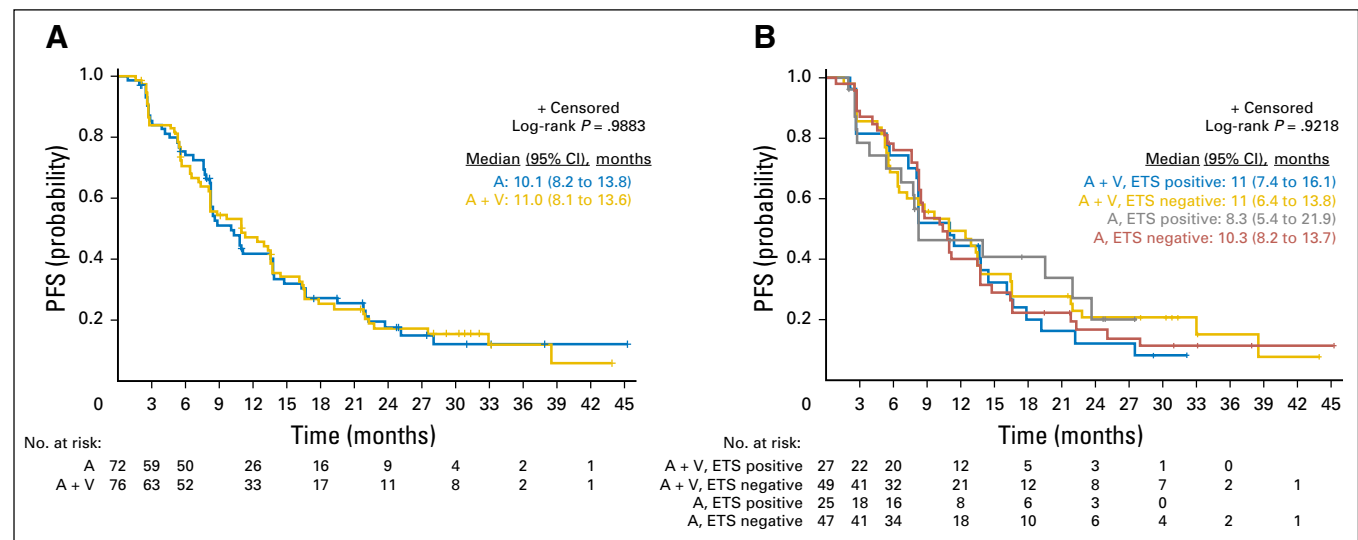


Fig A1. Progression-free survival (PFS) in patients with metastatic castration-resistant prostate cancer treated with abiraterone (A) or abiraterone plus veliparib (A + V) and stratified by ETS gene fusion status. (A) PFS curves are shown for all 148 response-evaluable patients treated with abiraterone/prednisone alone ($n = 72$) or in combination with veliparib ($n = 76$). (B) PFS curves are shown for each treatment arm stratified by ETS gene fusion status (determined by immunohistochemistry or in situ hybridization).

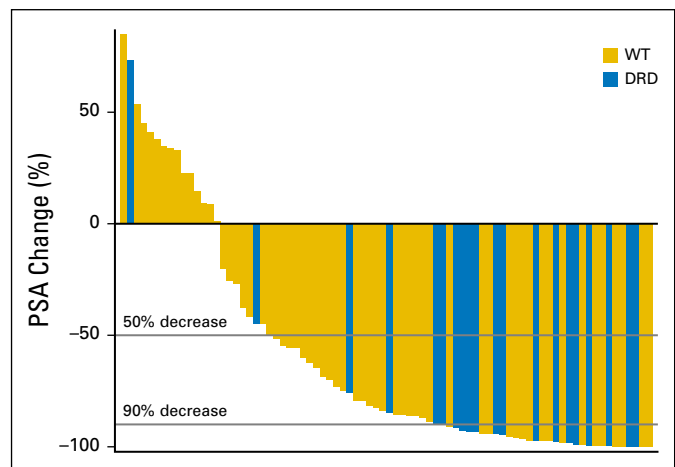


Fig A2. Depth of prostate-specific antigen (PSA) decline by DNA-damage repair defect (DRD) status. WT, wild type.

Table A1. Demographic and Clinical Characteristics of Patients by Tumor Sequencing Status			
Characteristic	No. (%)		<i>P</i>
	Sequenced (n = 80)	Not Sequenced (n = 68)	
Age, years			.44
Median	68	68	
Range	50-85	55-90	
Race			.67
White	69 (86.3)	62 (91.2)	
Black	7 (8.8)	4 (5.9)	
Other	4 (5.0)	2 (2.9)	
Performance status			.88
0	50 (62.5)	43 (63.2)	
1	29 (36.3)	25 (36.8)	
2	1 (1.3)	0	
PSA, ng/mL			.59
Median	36.8	31.0	
Range	0.04-1,557.6	0.5-940.7	
Cancer pain present	28 (35.0)	18 (26.5)	.26
Sites of disease			
Bone	66 (82.5)	62 (91.2)	.12
Lymph node	62 (77.5)	33 (48.5)	< .001
Visceral	20 (25.0)	14 (20.6)	.52
Other	15 (18.8)	13 (19.1)	.95
Previous treatment			
Chemotherapy	25 (31.3)	13 (19.1)	.09
Docetaxel/cabazitaxel	17 (21.3)	10 (14.7)	
Other	8 (10.0)	3 (4.4)	
Enzalutamide	2 (2.5)	2 (2.9)	.99
Sipuleucel-T	19 (23.8)	15 (22.1)	.85
Experimental agent	18 (22.5)	16 (23.5)	.88
Strata: ETS fusion and ketoconazole use			< .001
ETS fusion positive*	39 (48.8)	13 (19.1)	
ETS fusion negative	41 (51.3)	55 (80.9)	
Previous ketoconazole	10 (12.5)	6 (8.8)	.60
Treatment arm			.05
Abiraterone	33 (41.3)	39 (57.4)	
Abiraterone + veliparib	47 (58.8)	29 (42.7)	
No. of treatment cycles			.79
Median	9	9	
Range	2-50	1-46	
PSA response rate, %	65.0	72.1	.36
Measurable disease	60 (75.0)	26 (38.2)	< .001
Objective response, %	51.7	42.3	.43
PFS, months			.47
Median	10.3	10.8	
95% CI	8.0 to 13.8	8.2 to 13.7	
OS, months			.90
Median	32.3	30.6	
95% CI	24.1 to NR	28.1 to NR	

Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.
 *ETS fusion determined by immunohistochemistry/in situ hybridization.

Table A2. Baseline Covariates Among Patients With Tumor Sequencing

Characteristic	No. (%)		<i>P</i>
	Abiraterone (n = 33)	Abiraterone + Veliparib (n = 47)	
Age, years			.22
Median	70	68	
Range	50-80	52-86	
Race			.61
White	27 (81.8)	42 (89.4)	
Black	4 (12.1)	3 (6.4)	
Other	2 (6.1)	2 (4.3)	
Performance status			.50
0	19 (57.6)	31 (66.0)	
1	14 (42.4)	15 (31.9)	
2	0	1 (2.1)	
PSA, ng/mL			.87
Median	35.2	39.2	
Range	2-1,557.6	0.04-785.8	
Cancer pain present	14 (42.4)	14 (29.8)	.24
Sites of disease			
Bone	15 (45.5)	27 (57.5)	.29
Lymph node	24 (72.7)	38 (80.9)	.39
Visceral	6 (18.2)	14 (29.8)	.18
Other	6 (18.2)	9 (19.2)	.91
Previous treatments			
Chemotherapy	9 (27.3)	16 (34.0)	.52
Docetaxel/cabazitaxel	5 (15.2)	12 (25.5)	
Other	4 (12.1)	4 (8.5)	
Enzalutamide	1 (3.0)	1 (2.1)	.99
Sipuleucel-T	12 (36.4)	7 (14.9)	.03
Experimental agent	8 (24.2)	10 (21.3)	.75
Strata: ETS fusion and ketoconazole use			.68
ETS fusion positive	17 (51.5)	22 (46.8)	
ETS fusion negative	16 (48.5)	25 (53.2)	
Previous ketoconazole	5 (15.2)	5 (10.6)	.73
No. of treatment cycles			.58
Median	9	9	
Range	2-39	2-50	
Confirmed PSA response	18 (54.6)	34 (72.3)	.10
Measurable disease response	11 (45.8)	20 (55.6)	.46
PFS, months			.89
Median	8.8	11.0	
95% CI	6.7 to 13.8	7.4 to 13.8	
OS, months			—
Median	29.4	32.3	
95% CI	17.4 to NR	24.1 to NR	

Abbreviations: NR, not reached; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen.

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Table A3. AEs by Treatment Arm

AE	No. (%)											
	Arm A: Abiraterone (n = 74)						Arm B: Abiraterone + Veliparib (n = 79)					
	Grade						Grade					
	1	2	3	4	5	Total	1	2	3	4	5	Total
ALT increased	8 (11)	1 (1)	3 (4)	0 (0)	0 (0)	12 (16)	4 (5)	0 (0)	2 (3)	0 (0)	0 (0)	6 (8)
Alkaline phosphatase increased	3 (4)	2 (3)	0 (0)	0 (0)	0 (0)	5 (7)	2 (3)	4 (5)	2 (3)	0 (0)	0 (0)	8 (10)
Anemia	9 (12)	1 (1)	1 (1)	0 (0)	0 (0)	11 (15)	10 (13)	4 (5)	2 (3)	0 (0)	0 (0)	16 (20)
Anorexia	3 (4)	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)	5 (6)	5 (6)	0 (0)	0 (0)	0 (0)	10 (13)
Arthralgia	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	2 (3)
AST increased	14 (19)	2 (3)	0 (0)	0 (0)	0 (0)	16 (22)	6 (8)	2 (3)	0 (0)	0 (0)	0 (0)	8 (10)
Atrial fibrillation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Cardiac arrest	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Confusion	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Dehydration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	1 (1)	0 (0)	0 (0)	3 (4)
Diarrhea	4 (5)	1 (1)	0 (0)	0 (0)	0 (0)	5 (7)	10 (13)	2 (3)	0 (0)	0 (0)	0 (0)	12 (15)
Dizziness	2 (3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	7 (9)	1 (1)	0 (0)	0 (0)	0 (0)	8 (10)
Edema limbs	13 (18)	2 (3)	0 (0)	0 (0)	0 (0)	15 (20)	5 (6)	0 (0)	0 (0)	0 (0)	0 (0)	5 (6)
Ejection fraction decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Fatigue	18 (24)	2 (3)	0 (0)	0 (0)	0 (0)	20 (27)	31 (39)	8 (10)	0 (0)	0 (0)	0 (0)	39 (49)
Glucose intolerance	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Headache	6 (8)	0 (0)	0 (0)	0 (0)	0 (0)	6 (8)	5 (6)	1 (1)	1 (1)	0 (0)	0 (0)	7 (9)
Heart failure	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hot flashes	8 (11)	1 (1)	0 (0)	0 (0)	0 (0)	9 (12)	16 (20)	0 (0)	0 (0)	0 (0)	0 (0)	16 (20)
Hyperglycemia	3 (4)	1 (1)	6 (8)	1 (1)	0 (0)	11 (15)	6 (8)	2 (3)	4 (5)	0 (0)	0 (0)	12 (15)
Hypertension	2 (3)	6 (8)	3 (4)	0 (0)	0 (0)	11 (15)	3 (4)	2 (3)	3 (4)	0 (0)	0 (0)	8 (10)
Hypokalemia	6 (8)	0 (0)	0 (0)	0 (0)	0 (0)	6 (8)	7 (9)	1 (1)	1 (1)	0 (0)	0 (0)	9 (11)
Hypophosphatemia	3 (4)	4 (5)	1 (1)	0 (0)	0 (0)	8 (11)	2 (3)	4 (5)	1 (1)	0 (0)	0 (0)	7 (9)
Hypotension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Insomnia	4 (5)	0 (0)	0 (0)	0 (0)	0 (0)	4 (5)	8 (10)	2 (3)	1 (1)	0 (0)	0 (0)	11 (14)
Lymphocyte count decreased	3 (4)	1 (1)	1 (1)	0 (0)	0 (0)	5 (7)	6 (8)	8 (10)	1 (1)	0 (0)	0 (0)	15 (19)
Nausea	5 (7)	0 (0)	0 (0)	0 (0)	0 (0)	5 (7)	29 (37)	12 (15)	1 (1)	0 (0)	0 (0)	42 (53)
Pain	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	2 (3)	1 (1)	1 (1)	0 (0)	0 (0)	4 (5)
Platelet count decreased	2 (3)	1 (1)	0 (0)	0 (0)	0 (0)	3 (4)	5 (6)	1 (1)	1 (1)	1 (1)	0 (0)	8 (10)
Respiratory, thoracic, and mediastinal disorders—other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Sinus tachycardia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Syncope	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Thromboembolic event	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)	0 (0)	2 (3)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	12 (15)	5 (6)	0 (0)	0 (0)	0 (0)	17 (22)
Maximum grade for patient	27 (36)	15 (20)	15 (20)	1 (1)	0 (0)	58 (78)	24 (30)	28 (35)	19 (24)	1 (1)	1 (1)	73 (92)

Abbreviation: AE, adverse event.

Table A4. ETS Gene Fusion Agreement Between Trial Methods and Sequencing

ETS Status by Trial Methods*	ETS Status by Sequencing No. (%)	
	Negative	Positive
Negative	36 (45.0)	5 (6.25)
Positive	3 (3.75)	36 (45.0)
Agreement	72 (90) of 80	

*Trial methods: immunohistochemistry and in situ hybridization/fluorescence in situ hybridization.

Table A5. Biomarker Prognostic Analysis: Overall PSA Response, Measurable Disease Response, and PFS by Biomarker Status

Response/PFS	Biomarker Status		P
	Not Normal	Normal	
Confirmed PSA response		No. (%)	
ETS (positive [n = 41] v negative [n = 39])	25 (61.0)	27 (69.2)	.44
DNA repair (defect [n = 20] v WT/monoallelic [n = 60])	18 (90.0)	34 (56.7)	.007
AR (amplified/mutated [n = 41] v normal [n =39])	25 (61.0)	27 (69.2)	.44
TP53 (mutated [n = 33] v normal [n = 47])	20 (60.6)	32 (68.1)	.49
PTEN (mutated [n = 34] v normal [n = 46])	17 (50.0)	35 (76.1)	.016
PIK3CA pathway (activated [n = 39] v normal [n = 41])	22 (56.4)	30 (73.2)	.12
WNT pathway (activated [n = 12] v normal [n = 68])	8 (66.7)	44 (64.7)	.99
RB1 (mutated [n = 9] v normal [n = 71])	6 (66.7)	46 (64.8)	.99
CHD1 (mutated [n = 4] v normal [n = 76])	3 (75.0)	49 (64.5)	.99
SPOP (mutated [n = 5] v normal [n = 75])	4 (80.0)	48 (64.0)	.65
ZFHX3 (mutated [n = 6] v normal [n = 74])	3 (50.0)	49 (66.2)	.42
Measurable disease response			
ETS (positive [n = 31] v negative [n = 29])	15 (48.4)	16 (55.2)	.60
DNA repair (defect [n = 16] v WT/monoallelic [n = 44])	14 (87.5)	17 (38.6)	.001
AR (amplified/mutated [n = 29] v normal [n = 31])	13 (44.8)	18 (58.1)	.31
TP53 (mutated [n = 24] v normal [n = 36])	10 (41.7)	21 (58.3)	.21
PTEN (mutated [n = 28] v normal [n = 32])	12 (42.9)	19 (59.4)	.20
PIK3CA pathway (activated [n = 29] v normal [n = 31])	13 (44.8)	18 (58.1)	.31
WNT pathway (activated [n = 8] v normal [n = 52])	3 (37.5)	28 (53.9)	.47
RB1 (mutated [n = 4] v normal [n = 56])	2 (50.0)	29 (51.8)	.99
CHD1 (mutated [n = 3] v normal [n = 57])	2 (66.7)	29 (50.9)	.99
SPOP (mutated [n = 4] v normal [n = 56])	3 (75.0)	28 (50.0)	.61
ZFHX3 (mutated [n = 5] v normal [n = 55])	3 (60.0)	28 (50.9)	.99
PFS, months		Median (95% CI)	
ETS (positive [n = 41] v negative [n = 39])	8.2 (5.4 to 14.5)	13.3 (8.2 to 13.8)	.48
DNA repair (defect [n = 20] v WT/monoallelic [n = 60])	14.5 (11.0 to 19.5)	8.1 (5.5 to 11.0)	.025
AR (amplified/mutated [n = 41] v normal [n = 39])	8.8 (5.4 to 13.5)	11.0 (8.0 to 16.6)	.17
TP53 (mutated [n = 33] v normal [n = 47])	7.7 (5.3 to 8.8)	13.5 (8.2 to 16.6)	.01
PTEN (mutated [n = 34] v normal [n = 46])	6.7 (4.1 to 11.3)	13.5 (8.2 to 16.6)	.02
PIK3CA pathway (activated [n = 39] v normal [n = 41])	8.3 (5.4 to 13.3)	13.8 (8.2 to 16.6)	.03
WNT pathway (activated [n = 12] v normal [n = 68])	12.4 (2.7 to 23.7)	10.3 (8.0 to 13.6)	.91
RB1 (mutated [n = 9] v normal [n = 71])	8.8 (1.9 to 23.7)	10.3 (8.0 to 13.8)	.46
CHD1 (mutated [n = 4] v normal [n = 76])	NR (2.6 to NR)	8.8 (7.8 to 13.6)	.09
SPOP (mutated [n = 5] v normal [n = 75])	NR (2.8 to NR)	8.8 (7.8 to 13.6)	.06
ZFHX3 (mutated [n = 6] v normal [n = 74])	10.0 (2.1 to 13.8)	10.3 (8.0 to 13.8)	.20

Abbreviations: NR, not reached; PFS, progression-free survival; PSA, prostate-specific antigen.

Targeting AR and DNA Repair in CRPC

Table A6. Biomarker Predictive Analysis: Overall PSA Response, Measurable Disease Response, and PFS by Biomarker Status and Treatment Arm

Response/PFS	Marker Not Normal			Marker Normal			Interaction <i>P</i>
	Abiraterone	Abiraterone + Veliparib	<i>P</i>	Abiraterone	Abiraterone + Veliparib	<i>P</i>	
Confirmed PSA response	No. (%)			No. (%)			
ETS (positive [n = 41] v negative [n = 39])	8 (44.4)	17 (73.9)	.05	10 (66.7)	17 (70.8)	.78	.27
DNA repair (defect [n = 20] v WT/monoallelic [n = 60])	6 (85.7)	12 (92.3)	1.0	12 (46.2)	22 (64.7)	.15	.97
AR (amplified/mutated [n = 41] v normal [n = 39])	9 (47.4)	16 (72.7)	.097	9 (64.3)	18 (72.0)	.72	.45
PTEN (mutated [n = 34] v normal [n = 46])	5 (35.7)	12 (60.0)	.16	13 (68.4)	22 (81.5)	.31	.78
TP53 (mutated [n = 33] v normal [n = 47])	9 (60.0)	11 (61.1)	.95	9 (50.0)	23 (79.3)	.036	.18
PIK3CA pathway (activated [n = 39] v normal [n = 41])	6 (40.0)	16 (66.7)	.10	12 (66.7)	18 (78.3)	.41	.60
WNT pathway (activated [n = 12] v normal [n = 68])	3 (42.9)	5 (100.0)	.08	15 (57.7)	29 (69.1)	.34	.95
Measurable disease response	No. (%)			No. (%)			
ETS (positive [n = 31] v negative [n = 29])	6 (42.9)	9 (52.9)	.58	5 (50.0)	11 (57.9)	.68	.94
DNA repair (defect [n = 16] v WT/monoallelic [n = 44])	4 (80.0)	10 (90.9)	1.00	7 (36.8)	10 (40.0)	.83	.64
AR (amplified/mutated [n = 29] v normal [n = 31])	4 (36.4)	9 (50.0)	.70	7 (53.9)	11 (61.1)	.69	.81
PTEN (mutated [n = 28] v normal [n = 32])	5 (45.5)	7 (41.2)	.82	6 (46.2)	13 (68.4)	.21	.31
TP53 (mutated [n = 24] v normal [n = 36])	5 (50.0)	5 (35.7)	.68	6 (42.9)	15 (68.2)	.18	.14
PIK3CA pathway (activated [n = 29] v normal [n = 31])	5 (45.5)	8 (44.4)	.96	6 (46.2)	12 (66.7)	.25	.41
WNT pathway (activated [n = 8] v normal [n = 52])	0 (0.0)	3 (75.0)	.14	11 (55.0)	17 (53.1)	.90	.97
PFS, months	Median (95% CI)			Median (95% CI)			
ETS (positive [n = 41] v negative [n = 39])	7.7 (2.7 to 19.5)	11.0 (7.4 to 17.9)	.29	13.8 (8.2 to 16.6)	11.0 (5.5 to 13.8)	.33	.20
DNA repair (defect [n = 20] v WT/monoallelic [n = 60])	16.6 (13.5 to 19.5)	13.8 (8.2 to 32.9)	.93	8.2 (3.9 to 10.3)	8.1 (5.3 to 13.6)	.79	.89
AR (amplified/mutated [n = 41] v normal [n = 39])	8.3 (2.8 to 16.6)	8.8 (5.4 to 13.8)	.87	10.3 (6.7 to NR)	11.0 (6.4 to 17.9)	.60	.52
PTEN (mutated [n = 34] v normal [n = 46])	6.7 (2.6 to 19.5)	6.9 (2.8 to 13.6)	.55	13.5 (7.8 to 16.6)	13.8 (8.1 to 19.2)	.69	.40
TP53 (mutated [n = 33] v normal [n = 47])	8.3 (3.9 to 13.8)	5.7 (2.8 to 8.8)	.30	13.5 (2.7 to 16.6)	13.8 (8.2 to 17.9)	.84	.31
PIK3CA pathway (activated [n = 39] v normal [n = 41])	8.3 (2.6 to 19.5)	11.0 (5.3 to 13.6)	.62	13.8 (7.7 to 16.6)	13.8 (7.4 to 22.2)	.77	.51
WNT pathway (activated [n = 12] v normal [n = 68])	8.3 (1.9 to 23.7)	16.5 (5.4 to 32.9)	.74	8.8 (5.4 to 13.8)	11.0 (7.4 to 13.8)	.85	.80

NOTE. Markers included but too small of a mutation/aberrant representative sample size by treatment arm for analysis: *RB1*, *CHD1*, *SPOP*, and *ZFX3*. Abbreviations: NR, not reached; PFS, progression-free survival; PSA, prostate-specific antigen.

Table A7. Multivariable Analysis of PFS

Covariate	Hazard Ratio (95% CI)		
	Unadjusted Univariable Analysis		Multivariable Cox Model
	All Patients	Sequenced Patients Only	Sequenced Patients Only
Clinical			
Treatment arm			
Abiraterone + veliparib v abiraterone	1.00 (0.70 to 1.44)	1.04 (0.62 to 1.72)	1.00 (0.58 to 1.72)
ETS fusion status			
Positive v negative	1.06 (0.72 to 1.56)	1.19 (0.73 to 1.95)	1.05 (0.60 to 1.83)
Prior ketoconazole	1.96 (1.11 to 3.46)	1.62 (0.79 to 3.31)	1.57 (0.74 to 3.36)
Age	1.02 (1.00 to 1.05)	1.04 (1.002 to 1.07)	1.04 (1.00 to 1.08)
Race			
Black v white	0.87 (0.44 to 1.73)	0.58 (0.23 to 1.44)	0.49 (0.18 to 1.34)
Other v white	0.65 (0.24 to 1.78)	0.35 (0.09 to 1.44)	0.29 (0.07 to 1.31)
Performance status			
Symptomatic v normal	2.00 (1.37 to 2.92)	2.27 (1.35 to 3.80)	2.02 (1.16 to 3.53)
Baseline PSA (log transformed)	1.13 (1.00 to 1.27)	1.09 (0.92 to 1.29)	1.02 (0.88 to 1.19)
Previous chemotherapy	2.09 (1.39 to 3.13)	2.19 (1.31 to 3.66)	2.00 (1.12 to 3.54)
Previous enzalutamide	5.48 (1.98 to 15.2)	Inf (2.0 to Inf)	—
Biomarkers*			
DNA repair (defect v WT/monoallelic)		0.52 (0.29 to 0.93)	0.51 (0.27 to 0.97)
AR (amplified/mutated v normal)		1.41 (0.86 to 2.31)	1.34 (0.80 to 2.23)
TP53 (mutated v normal)		1.88 (1.14 to 3.12)	2.52 (1.30 to 4.89)
PTEN (mutated v normal)		1.82 (1.11 to 3.01)	1.61 (0.92 to 2.82)
PIK3CA pathway (activated v normal)		1.74 (1.05 to 2.87)	1.45 (0.79 to 2.68)
WNT pathway (activated v normal)		0.96 (0.50 to 1.85)	0.88 (0.44 to 1.74)
RB1 (mutated v normal)		1.32 (0.62 to 2.78)	1.47 (0.66 to 3.28)
CHD1 (mutated v normal)		0.31 (0.07 to 1.29)	0.39 (0.09 to 1.71)
SPOP (mutated v normal)		0.28 (0.07 to 1.15)	0.54 (0.09 to 3.40)
ZFX3 (mutated v normal)		1.74 (0.74 to 4.09)	1.44 (0.57 to 3.63)
ETS fusion by sequencing (positive v negative)		1.19 (0.73 to 1.95)	1.24 (0.45 to 3.38)

Abbreviations: PFS, progression-free survival; PSA, prostate-specific antigen.

*Biomarkers were added separately and individually to the multivariable model containing clinical covariates.

Table A8. Exceptional Responder Data

Patient ID	Site	Age (years)	Race	Treatment Group	ETS Fusions	DRD		Mutated			Activated		Mutated		Prior Treatments			PFS		PSA (ng/mL)				Metastatic Biopsy Site	Disease Site	Bone Disease	Maximum Change in Measurable Disease (%)	Type of Lesion	RECIST Comments	
						DRD	Genes	AR	PTEN	TP53	PI3K	WNT	SPOP	CHD1	Chemotherapy	Other	Ketoconazole	Months	Progression (I) or Censored (I)	Baseline	Nadir	Maximum Change (%)	Confirmed Response			Confirmed CR				No. of Lesions at Baseline
Sequenced																														
43	UM	72	White	A + V	–	DRD BA	BRCA2	Y	N	N	N	N	N	Y	None	N	N	44	0	112.9	0.1	–100	Y	Y	Liver	Bone and visceral	2-4	–80	2 hepatic masses and 2 iliac LNs	1 hepatic mass had 80% reduction in size, and other hepatic mass decreased in size by 76%; 1 LN returned to normal; 1 LN decreased by two thirds
53	COH	66	White	A + V	–	DRD BA	BRCA2	N	N	N	N	N	N	N	None	N	N	39	1	16.39	0.04	–100	Y	Y	LN	Bone and visceral	2-4	–81	5 LNs	2 retroperitoneal LNs returned to normal; nontarget pulmonary nodule remained stable; progression by new liver metastases
85	UM	53	Black	A + V	+	DRD BA	RAD51B, RAD51C	N	N	N	N	Y	N	N	Other	N	N	33	1	55.2	3.9	–93	Y	N	LN	Bone ± LN	5-9	–57	1 LN	Lateral external iliac LN mass; progression in LN mass
119	MDA	58	White	A + V	+	DRD BA	BRCA2	N	N	N	N	N	N	N	Doc/cab	N	N	29	0	8.8	0.5	–94	Y	N	LN	Bone and visceral	5-9	–46	2 masses; 1 LN	2 masses reduced approximately 40% each; LN shrank by 56%
125	COH	60	White	A + V	–	DRD MA	BRCA1	N	N	N	N	N	N	N	None	Y	N	31	0	33.86	2.05	–94	Y	N	LN	Visceral or other	0	–90	1 mass	Pubic ramus-associated soft tissue
34	COH	80	Other	A	–	WT		N	N	N	N	N	Y	N	None	Y	N	33	0	25.68	0.0	–100	Y	Y	LN	Visceral or other	0	–100	Left upper lung nodule and 3 LNs	Lung nodule went from 11 at baseline to 0 at 3-month scan; LNs decreased from first scan through 19.5-month scan when CR was attained; CR was confirmed 3 months after initial CR (22.5 months on trial)
70	COH	72	White	A	+	WT		CG	Y	Y	Y	N	N	N	None	Y	N	25	0	39.74	0.13	–100	Y	Y	LN	LN only	0	–32	3 LNs	1 LN remained stable; 2 decreased; patient continued receiving A after departing trial after 1 year and remained stable in follow-up
82	COH	62	White	A+V	+	WT		Amp	Y	Y	Y	N	N	N	None	Y	N	27	1	1.92	0.0	–100	Y	Y	LN	Visceral or other	0	–58		1 nodule reduced by 40%; 1 LN reduced to normal; 1 LN decreased and remained stable
107	UNC	75	Black	A	–	WT		N	Y	N	Y	N	Y	N	None	N	N	31	0	35.2	0.1	–100	Y	Y	LN	Bone ± LN	1	–64	2 LNs	1 LN reduced from 33 to 11, and other LN reduced from 14 to 6
Not sequenced																														
40	CINJ	64	White	A	+	ND									None	N	N	27	0	20.87	0.42	–98	Y	N	Bone	Bone ± LN	2-4			
44	COH	70	White	A + V	–	ND									None	N	N	28	0	2.41	0	–100	Y	Y	Bone	Bone ± LN	> 20			
49	IU	74	White	A	–	ND									None	N	N	45	0	93.942	0.008	–100	Y	Y	Bone	Bone ± LN	> 20			
77	NS	65	White	A	–	ND									None	Y	N	38	0	6.36	0.02	–100	Y	Y	Bone	Bone ± LN	2-4			
102	COH	61	White	A + V	–	ND									None	Y	N	33	0	151.31	0	–100	Y	Y	Bone	Bone ± LN	5-9			
113	UWASH	67	White	A + V	–	ND									None	N	N	31	0	0.95	0.03	–97	Y	Y	Bone	Bone ± LN	5-9			
132	CINJ	62	White	A + V	+	ND									None	Y	N	32	0	159.5	1.46	–99	Y	N	Bone	Bone ± LN	5-9			
138	COH	74	White	A + V	–	ND									None	Y	N	30	0	1.22	0	–100	Y	Y	Bone	Bone ± LN	5-9			
146	UM	62	White	A	+	ND									None	N	N	25	0	11	0.1	–99	Y	Y	LN	LN only	0			
162	UM	60	White	A	–	ND									None	N	N	25	1	9.7	0.1	–99	Y	Y	Bone	Bone and visceral	10-20			

NOTE. Exceptional responders were patients with > 24 months PFS and > 90% PSA response.
Abbreviations: A, abiraterone; amp, amplified; BA, biallelic; cab, cabozantinib; CG, copy gain; CINJ, Cancer Institute of New Jersey; COH, City of Hope; CR, complete response; doc, docetaxel; DRD, DNA-damage repair defect; IU, Indiana University; LN, lymph node; MA, monoallelic; MDA, MD Anderson; ND, not determined; NS, NorthShore; PFS, progression-free survival; PSA, prostate-specific antigen; RECIST, Response Evaluation Criteria in Solid Tumors; UM, University of Michigan; UNC, University of North Carolina; UWASH, University of Washington; V, veliparib; WT, wild type.

REVIEW

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Prostate cancer and PARP inhibitors: progress and challenges

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Abstract

Despite survival improvements achieved over the last two decades, prostate cancer remains lethal at the metastatic castration-resistant stage (mCRPC) and new therapeutic approaches are needed. Germinal and/or somatic alterations of DNA-damage response pathway genes are found in a substantial number of patients with advanced prostate cancers, mainly of poor prognosis. Such alterations induce a dependency for single strand break reparation through the poly(adenosine diphosphate-ribose) polymerase (PARP) system, providing the rationale to develop PARP inhibitors. In solid tumors, the first demonstration of an improvement in overall survival was provided by olaparib in patients with mCRPC harboring homologous recombination repair deficiencies. Although this represents a major milestone, a number of issues relating to PARP inhibitors remain. This timely review synthesizes and discusses the rationale and development of PARP inhibitors, biomarker-based approaches associated and the future challenges related to their prescription as well as patient pathways.

Keywords: PARP inhibitors, Prostate cancers, Homologous recombination repair, DNA repair

Background

Prostate cancer is the second most common malignancy and the fifth cause of cancer death in men, worldwide [1]. Despite survival improvements achieved using next generation hormonal therapies, chemotherapies or radionuclides [2], prostate cancer remains lethal at the metastatic castration resistant stage (mCRPC). While androgen-receptor (AR) signaling still plays a central role in their development [3], a better understanding of the genomic landscape has highlighted that DNA-damage response (DDR) pathways may contribute to the progression of a large number of advanced prostate cancers [4, 5] often associated with worse prognosis [6].

DDR gene alteration induces a dependency on poly(adenosine diphosphate-ribose) polymerase (PARP)-1 for DNA repair, leading to cancer cell death

when PARP-1 is inhibited. This synthetic lethality provides the rationale for using PARP inhibitors. Such treatments have already shown substantial survival benefits as maintenance therapy for patients with ovarian and pancreatic cancers or used in front line therapy in patients with breast cancers [7–9]. While several PARP inhibitors are still under development in prostate cancer, olaparib has just demonstrated an improvement in overall survival in patients with mCRPC harboring homologous recombination repair deficiency [10].

While this represents a major milestone to achieve, many issues remain unresolved regarding the efficacy of other PARP inhibitors, the potential toxicity of combinations, the panel of biomarkers to use, the mechanisms of resistance or the promising role of platinum salt-based chemotherapies. This review synthesizes and discusses the main points regarding the rationale and development of PARP inhibitors, the biomarker-based approaches associated and the future challenges related to their prescription as well as the patient's pathway.

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From DNA-damage repair to the homologous recombination deficiency in advanced prostate cancer

DNA-damage repair

DNA-maintenance machinery allows genome stability and prevents oncogenesis [11]. Single-strand breaks (e.g., insertion, deletion and mismatches) (SSBs) are repaired using base excision repair (BER), nucleotide excision repair (NER) or mismatch repair (MMR) processes. Those mechanisms are activated by various regulatory factors such as poly ADP-ribose polymerase (PARP), an ADP-ribosyl transferase, which contribute to recruit BER or NER proteins on the DNA strand break depending on the complexity of the point mutation.

PARP is a family of 17 distinct proteins, in which PARP 1 and 2 are involved in DNA repair [12]. PARP1 binds to damaged DNA gaps and, after conformational change, induces PARylation [13]. PARP1 catalyzes the polymerization of ADP-ribose units from NAD⁺ (nicotinamide adenine dinucleotide) molecules and recruits proteins of the DNA SSB repair system (BER or NER systems) [14, 15]. Once a repair complex is recruited to SSB, PARP1 is released from DNA.

When PARP1 is deficient, SSB cannot be repaired [16]. Through the process of DNA replication, SSB converts into a double-strand breaks (DSB), and the DSB repair system is then required. Three mechanisms exist to repair DSB: non-homologous end joining (NHEJ), microhomology-mediated end joining (MMEJ) and homologous recombination repair (HRR) [17]. HRR is the most conservative of them, leading to a high-fidelity repair by avoiding loss of information with the use of the second chromosome as a template.

Homologous recombination repair (Fig. 1)

Following a DSB, ATM, a serine/threonine kinase, is recruited and activated at the site. ATM activates, via CHK2, a phosphorylation cascade of several targets including BRCA1 [18]. BRCA1 recruits PALB2 which attracts BRCA2 and RAD51 [19, 20]. This complex induces the transfer of the broken sequence to the respective undamaged sequence of the second chromosome, allowing DNA restoration through a complex cascade of many protein interactions. This core process is called homologous pairing by strand invasion [21]. BRCA1 can also be activated through the Fanconi Anemia (FANC) and BRIP1 pathway [22].

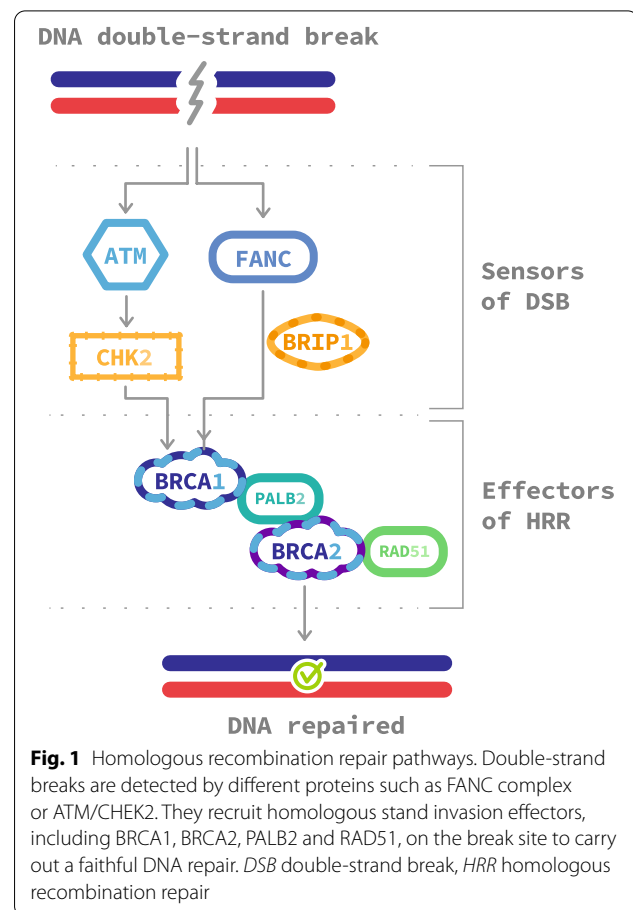


Fig. 1 Homologous recombination repair pathways. Double-strand breaks are detected by different proteins such as FANC complex or ATM/CHK2. They recruit homologous strand invasion effectors, including BRCA1, BRCA2, PALB2 and RAD51, on the break site to carry out a faithful DNA repair. DSB double-strand break, HRR homologous recombination repair

Homologous recombination deficiency in metastatic castration-resistant prostate cancer: prognostic impact of germinal mutations

Ninety percent of mCRPC carry at least one clinically actionable molecular alteration, with androgen receptor (AR) pathways being the most frequently altered (71%) [4]. Approximately 27% of mCRPC have a germline or a somatic alteration in *BRCA2*, *BRCA1*, *ATM* or *CHEK2* [5]. All HRR genes are tumor suppressors and require both alleles to be inactivated in the tumoral cell, with a complete loss of protein expression, according to the Knudson two-hit hypothesis. The first allele could either be constitutively or somatically inactivated. The second hit could be due to another somatic event, which leads to a complete loss of HRR system within the cell. A copy neutral loss of heterozygosity (LOH) with the loss of the wild-type allele is the most common phenomenon. When tumors are diagnosed with only one germline alteration without any other mutant allele (either by somatic mutation or LOH), HRR is still working and is not considered as a driver of oncogenesis [23]. Taking into account both somatic and germline mutations, *BRCA2* (12–18%), *ATM* (3–6%),

CHEK2 (2–5%) and *BRCA1* (<2%) are the most common altered genes involved in HRR [4, 5].

In a cohort of patients with mCRPC, 11.8% presented with a germline mutation in HRR genes, with an associated LOH in more than 90% of cases [24]. Interestingly, this cohort did not reveal any association with age and familial history of cancer, although most patients were younger than 70 years old [24]. These germline mutations represent roughly half of the cases of homologous recombination deficient (HRD) mCRPC [5]. *BRCA2* alterations are still the most frequent, responsible for 5.3% of cases, followed by *ATM*, *CHEK2* and *BRCA1* (1.9, 1.6 and 0.9%, respectively) [24].

Germline mutations of *BRCA1/2* and *ATM* are associated with worse prognosis in prostate cancer, while to-date, somatic mutations are not shown to be [6, 25]. Patients with germline *BRCA2* pathogenic variants have a 20-fold risk of death related to prostate cancer [26]. *ATM*, a DNA-damage sensor gene, is frequently altered in mCRPC. While a complete inactivation of *BRCA2*, *BRCA1* and *PALB2* imprints a distinct mutational signature on genomes, there is no such a pattern with *ATM* biallelic inactivation [27]. *CHEK2* is a checkpoint kinase gene, activated by *ATM* and regulating *BRCA1*. The most common pathogenic *CHEK2* mutation, c.1100delC, has been associated with an increased risk of lethal versus indolent prostate cancers (respectively, 1.28% vs. 0.16% $P=0.004$), giving a poor prognosis to this mutation [28]. Minor genes such as *BRIPI*, *RAD51D* or *PALB2* are found in less than 0.5% of cases [29, 30].

Deleterious *CDK12* alterations are enriched from localized to advanced prostate cancers, occurring in 5–11% of patients with mCRPC, and associated with worse prognosis and high Gleason scores [31–33]. *CDK12* is known to inhibit intronic polyadenylation sites (frequent in HRR genes sites), in order to keep the last exons within the transcript and avoid truncated proteins. While correlated to low expression of HRR genes, bi allelic *CDK12* inactivation was more recently shown to be associated with a distinct subgroup of prostate cancers characterized by focal tandem duplications and gene fusion-induced neoantigens all over the genome, as well as CD4+FOXP3—tumor-invasive lymphocytes (i.e., likely to be permissive) [28, 33]. In line with these pre-clinical data, a retrospective study suggested a better sensitivity of *CDK12* alterations to immune checkpoint inhibitors [31].

Alterations in HRR genes are present in a significant proportion of patients with mCRPC, but their clinical implication remains unclear. Recently, Castro et al. investigated the impact of germline mutations in HRR genes in the prospective PROREPAIR-B study [34]. DDR alterations were identified in 68 of 419 patients with mCRPC (16.2%), including 14 with *BRCA2*, 8 with *ATM*,

4 with *BRCA1* and none with *PALB2* or *CHEK2* mutations. The results did not show a difference in cause-specific survival (CSS) between altered and non-altered mCRPC ($P=0.65$). Conversely, CSS for patients with *BRCA2* alterations was approximately halved compared to non-carriers (17.4 months vs. 33.2 months, 95% CI 1.07–4.10, $P=0.27$). The authors conducted a post hoc analysis to compare the CSS and PFS2 (second progression or death) according to *BRCA2* status and sequence: taxane-new hormonal therapy (NHT) or NHT-taxane. After multivariate analysis it seemed that *gBRCA2* carriers had a shorter CSS and PFS2 compared to non-carriers in the taxane-NHT sequence, while no difference was observed in the NHT-taxane sequence. This suggests that *gBRCA2* alterations are correlated with poorer prognosis, but that NHT may reverse this effect. These results are reinforced by the retrospective study of Antonarakis et al., showing better progression-free survival (PFS) and overall survival (OS) in patients with *gBRCA/ATM* alterations treated with NHT as first line, compared to non-mutated patients. The outcomes after first line NHT did not appear better for patients with non-*BRCA/ATM* germline alterations [35]. The results of these two studies need to be confirmed with larger groups of patients. Similar studies regarding somatic HRR alterations were not found.

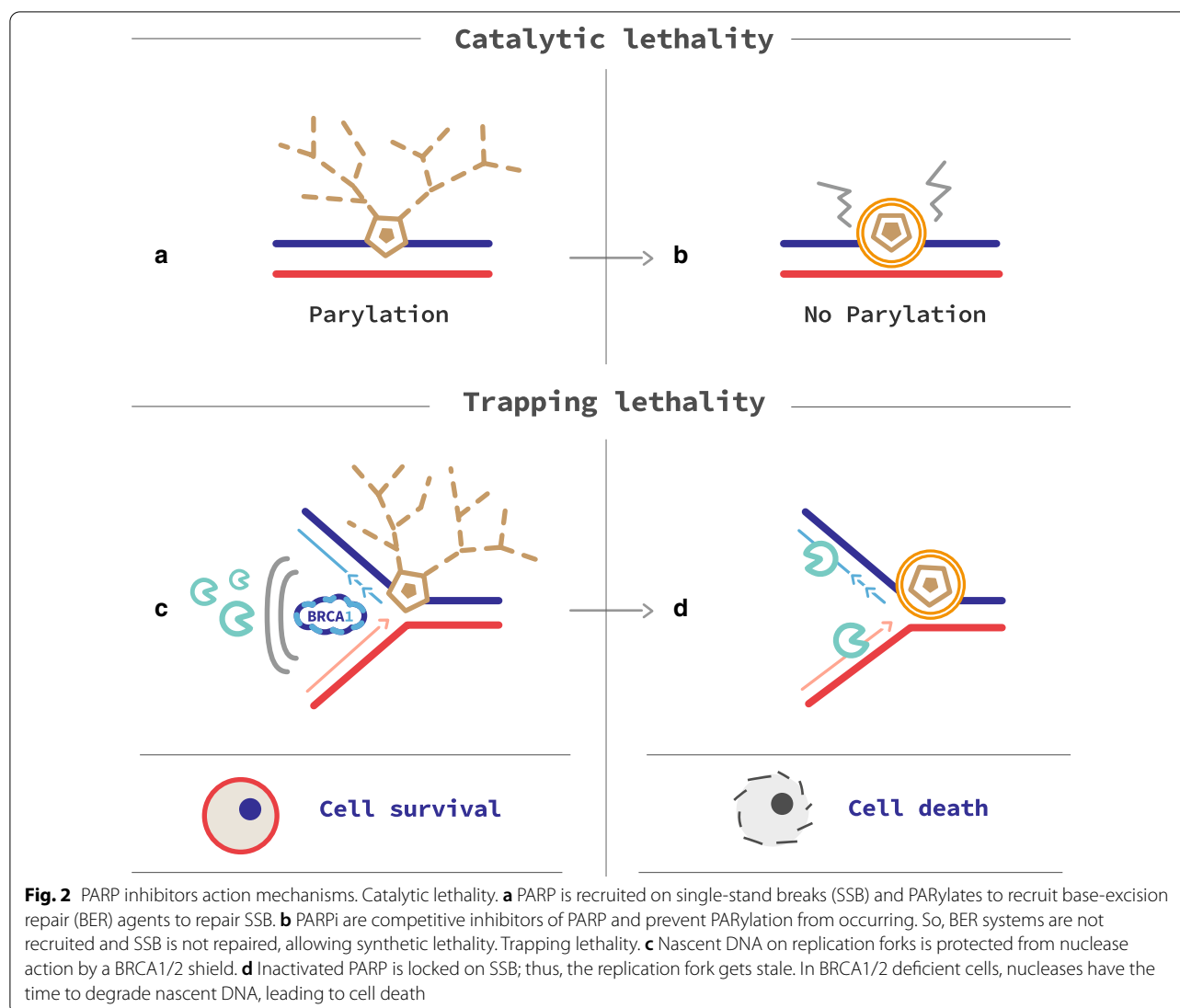
Overall, a growing body of evidence showing a poorer prognosis associated with germinal HRR gene aberrations as well as mitigated results of standard treatments in patients with prostate cancer, strengthened the rationale to develop specific treatments such as PARP inhibitors in this setting.

Development of PARP inhibitors in prostate cancer used alone or in combination

Mechanism

PARP inhibitors (PARPi) are oral-targeted therapies, which competitively bind to the NAD⁺ sites of PARP1 and PARP2 inducing a catalytic inhibition (Fig. 2a, b). Five different molecules are currently under development or recently approved: olaparib, rucaparib, niraparib, veliparib and talazoparib. Their action inhibits the PARylation, and thus, SSBs repair, leading to increase the number of SSB within the cell (Fig. 3a). Unrepaired SSB converts into DBS during the replication (Fig. 3b). When used on HRD cells, PARPi induce a synergistic lethal effect, increasing genomic instability enough to reach tumor cell death. This phenomenon is called synthetic lethality and is specific to tumor cells with complete HRD (Fig. 2c). Catalytic inhibition has been observed in prostate cancer cell lines [36, 37].

PARPi also trap PARP enzymes on DNA. The resulting DNA-PARP complexes block the replisome during



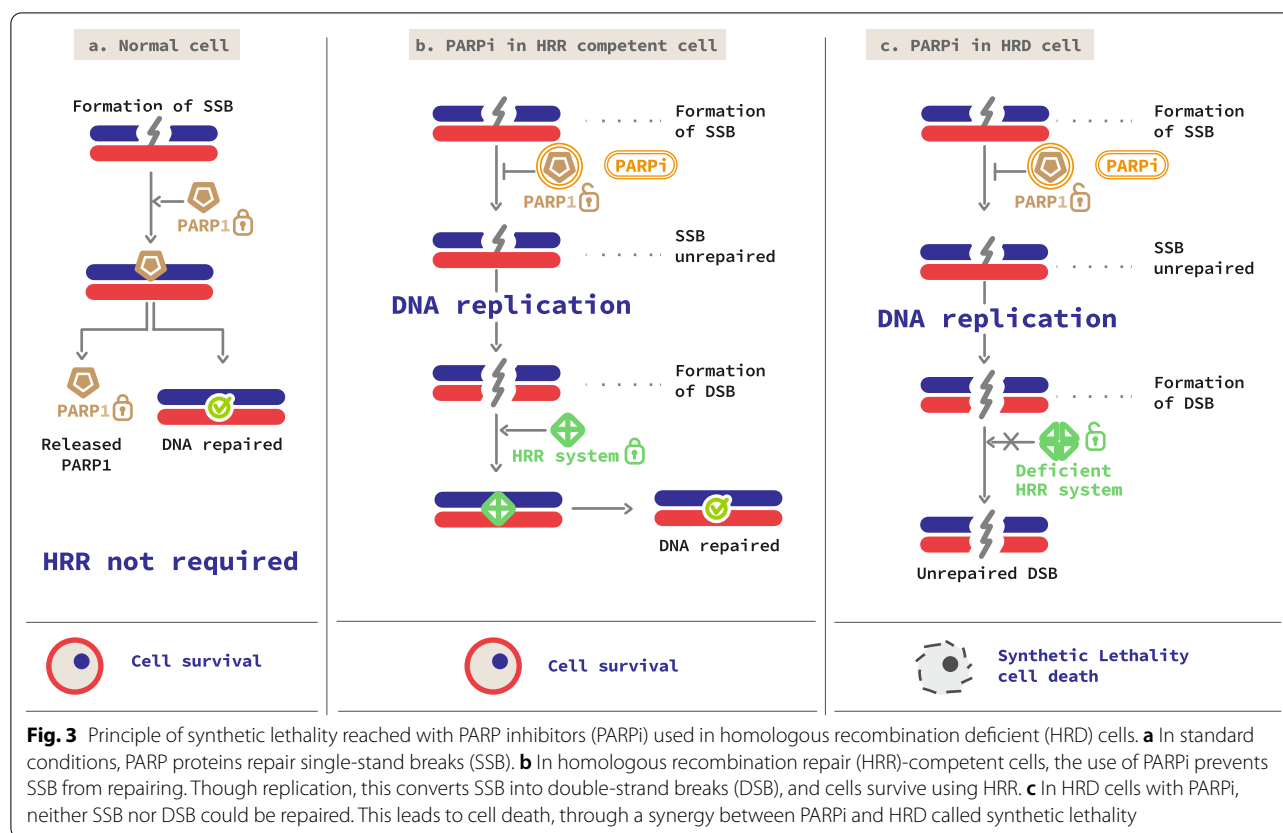
replication, in a way that only HRR can resolve (Fig. 2c, d) [36]. BRCA1, BRCA2 and PALB2 are not only involved in HRR, but also stabilize stalled replication forks. BRCA1/2 or PALB2 loss destabilizes replication forks, and this effect is potentialized by PARPi trapping, in a synthetic lethality process [38]. Thus, PARPi trapping has a cytotoxic action in HRD cells, and more accurately on BRCA1, BRCA2 or PALB2 deficient cells. Potency of trapping varies according to the molecule of PARPi used (e.g., major for talazoparib) [36, 37].

PARP inhibitors as single agents

According to the preclinical rationale described above, PARPi were firstly developed as single agents in mCRPC. The main clinical studies are summarized in Table 1.

Olaparib

Olaparib was the first PARPi to be described. After promising results reported in phase I, fifty patients with mCRPC were enrolled in a phase II study (TOPARP-A) [39]. They had received at least one chemotherapy regimen, and 98% were previously treated with abiraterone or enzalutamide. The primary *endpoint* was the composite response rate (CRR), defined as an objective radiological response (ORR) based on the response evaluation criteria in solid tumors (RECIST), or a reduction of at least 50% of the PSA level, or a decrease in the circulating tumor cell (CTC). Of the 49 patients assessed for CRR, seven had *BRCA2* and four had *ATM* alterations. Other HRR aberrations were seen in *BRCA1*, *CHEK2*, *FANCA*, *HDAC2* or *PALB2* genes. Fourteen of the 16 patients (88%) with HRR alterations had a CRR compared to 6% for the patients without HRR deficiencies. Olaparib was



well tolerated; grade 3 or 4 adverse events were primarily anemia (20%), fatigue (12%) and leukopenia (6%). Using next-generation sequencing (NGS), TOPARP-B selected 161 (27%) patients with HRR gene alterations among 592 patients with mCRPC treated with at least one chemotherapy, and eligible for NGS analysis, [40]. Given the dose/response relationship for olaparib [41, 42], ninety-eight patients were randomly assigned in 2 cohorts: one receiving olaparib 400 mg twice daily and the other 300 mg twice daily. The primary endpoint was CRR defined with the same criteria as TOPARP-A. A confirmed CRR was observed in 54.3% of the patients in the 400 mg arm, compared to 39.1% in the 300 mg cohort with, in return, higher toxicity in the 400 mg arm (3 times more patients requested a dose reduction in the arm 400 mg mostly due to anemia). A preplanned subgroup analysis showed that the highest CRR was observed in the *BRCA1/2* subgroup (83.3%), then *PALB2* (57.1%), both effectors of the HRR system. ORR was 52.4% and 33.3% for *BRCA1/2* and *PALB2* subgroups, respectively. The CRR was lower in the *ATM* and *CDK12* subgroups (36.8% and 25.0%, respectively), and moreover, almost no radiological or PSA responses were observed. The effect of olaparib in the *CDK12* subgroup might be influenced by an imbalance with more alterations in groups with

lower doses. While radiological and biological responses are commonly used in daily practice, the value of CTC conversion as a biomarker of response is still under evaluation, even if, in this trial, CTC conversion was associated with better radiographic PFS (rPFS) and OS. Thus, the CRR for the *ATM* and *CDK12* subgroups should be interpreted with caution.

TOPARP studies confirmed that Olaparib used alone was more efficient in HRR deficient mCRPC. Moreover, the efficacy in terms of CRR seemed to be higher for effector genes of the HRR system (*BRCA*, *PALB2*) than sensors (*ATM*, *CDK12*).

Building on these results, the PROfound study was designed [43]. This phase III trial compared olaparib to NHT in patients with mCRPC progressing after at least one treatment with enzalutamide or abiraterone. Previous taxane chemotherapy was allowed. Patients were included if an alteration (mono- or bi-allelic) in at least 1 of the 15 prespecified HRR genes (*BRCA1*, *BRCA2*, *ATM*, *BRIP1*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L*) was found. Patients with an alteration in *BRCA1*, *BRCA2* or *ATM* were assigned to cohort A, and patients with alterations in any of the 12 other genes were allocated to cohort B. The primary endpoint was the

Table 1 Phase II or III trials using PARP inhibitors alone to treat prostate cancers

CTID	Treatment	Phase	No. patients or estimated enrollment	Disease status	Mandatory HRR status for inclusion	Determination method for HRD	Primary endpoints	Results
NCT01682772/ TOPARP-A	Olaparib	2	50	mCRPC after at least docetaxel	No	Tumor	Composite response rate ^b	All comers: 33% HRD: 88%
NCT01682772/ TOPARP-B	Olaparib	2	98	mCRPC after at least docetaxel	Bi-allelic deleterious HRD	Tumor	Composite response rate ^b Preplanned secondary endpoint: ORR	<i>BRCA1/2</i> : 83%, ORR: 52.4% <i>PALB2</i> : 57%, ORR: 33.3% <i>ATM</i> : 37%, ORR: 8.3% <i>CDK12</i> : 25%, ORR: 0%
NCT02987543/PRO-found	Olaparib versus NHT	3	778	mCRPC after at least 1 NHT	Bi- or mono-allelic somatic or germline deleterious HRD	Tumor	Radiographic PFS Preplanned secondary endpoint: OS	rPFS: <i>BRCA/ATM</i> : 7.4 months versus 3.6mo, HR = 0.34 (95% CI 0.25–0.47) General HRD: 5.8 months versus 3.5 months, HR = 0.49 (95% CI 0.38–0.63) OS: <i>BRCA/ATM</i> : 19.1 months versus 14.7 months HR = 0.69 (CI 95% 0.5–0.97) No- <i>BRCA/ATM</i> : 14.1 months versus 11.5 months HR = 0.96 (CI 95% 0.63–1.49)
NCT03432897/ BrUOG-337	Olaparib	2	13	High-risk localized PC	Deleterious HRD ^a	Tumor or plasma	PSA response rate prior prostatectomy	Recruiting
NCT03047135	Olaparib	2	50	Castration Sensitive Biochemically Recurrent nmPC	No	Undescribed method	PSA response rate	Recruiting
NCT03434158 / IMANOL	Olaparib as maintenance therapy after docetaxel	2	27	mCRPC after at least docetaxel	Deleterious HRD ^a	Undescribed method	Radiographic PFS	Recruiting
NCT03012321/ <i>BRCA</i> - Away	Olaparib versus abiraterone versus abiraterone + olaparib	2	70	mCRPC, 1st line	No	Tumor	PFS	Recruiting
NCT03263650	Olaparib maintenance after cabazitaxel–carboplatin combination	2	123	Aggressive variant PC	No	Not performed	PFS	Ongoing, not recruiting

Table 1 (continued)

CTID	Treatment	Phase	No. patients or estimated enrollment	Disease status	Mandatory HRR status for inclusion	Determination method for HRD	Primary endpoints	Results
NCT02854436/GALA-HAD	Niraparib	2	291	mCRPC after at least 1 chemotherapy and 1 NHT	Bi-allelic HRD or germline pathogenic BRCA1/2 alteration ^b	Tumor or plasma	ORR	BRCA: 41% Non-BRCA: 9%
NCT04288687	Niraparib	2	18	mCRPC, platin sensitivity	Deleterious HRD ^a	Undescribed method	Radiographic PFS	Not yet recruiting
NCT04037254	ADT (24 months) + RT + niraparib (12 months)	2	180	High-risk localized PC	No	Not performed	Disease-free survival	Ongoing, not recruiting
NCT04030559	Niraparib for 3 months	2	30	High-risk localized PC, prior prostatectomy	Bi- or mono-allelic deleterious HRD	Undescribed method	Pathologic response rate	Recruiting
NCT02952534/TRI-TON-2	Rucaparib	2	193	mCRPC after at least 1 chemotherapy and 1 NHT	Bi- or mono-allelic somatic or germline deleterious HRD	Tumor or plasma	ORR and PSA response rate (PRR)	sBRCA1/2: 43.9%, PRR: 50.7% gBRCA1/2: 42.9%, PRR: 61.4% ATM: 10.5%, PRR: 4.1% CDK12: 0%, PRR: 6.7% CHEK12: 11.1%, PRR: 16.7%
NCT02975934/TRI-TON-3	Rucaparib versus NHT or docetaxel	3	400	mCRPC, after 1 NHT, 0 chemotherapy	Deleterious BRCA1/2 or ATM alteration ^a	Undescribed method	Radiographic PFS	Recruiting
NCT03413995/TRI-UMPH	Rucaparib	2	30	mCSPC unfit/unwilling ADT	Germline HRD alteration ^b	Undescribed method	PSA response rate	Recruiting
NCT03442556/PLATI-PARP	Rucaparib maintenance after docetaxel–carboplatin combination	2	20	mCRPC	Bi- or mono-allelic deleterious HRD	Tumor or plasma	Radiographic PFS	Recruiting
NCT03533946/ROAR	Rucaparib	2	32	nmCSPC	Deleterious HRD ^a	Tumor or plasma	PSA response rate	Recruiting
NCT03148795/TAL-APRO-1	Talazoparib	2	100	mCRPC after at least 1 chemotherapy and 1 NHT	Mono- or bi-allelic HRD (CDK12 excluded)	Tumor	ORR	BRCA: 50% ATM: 7% Other HRD: 0%

ATM: ataxia telangiectasia mutated, sBRCA: somatic deleterious mutation of BRCA, gBRCA: germinal deleterious mutation of BRCA, mCRPC metastatic castration-resistant prostate cancer, mCSPC metastatic castration-sensitive prostate cancer, nmPC non-metastatic prostate cancer, nmCSPC non-metastatic castration-sensitive prostate cancer, ADT androgen deprivation therapy, NHT new hormonal therapy, HRR homologous recombination repair, HRD homologous repair deficiency, CTID clinical trial identification, PC prostate cancer, PFS progression free survival, ORR objective response rate, PSA response rate: decline of more than 50%, RT radiotherapy

^a Mono- or bi-allelic status not specified

^b Germline or somatic alteration specified

^c Composite response rate: response according to RECIST or PSA reduction > 50%, or reduction of circulating tumor cells to less than 5/7.5 mL of blood confirmed 4 weeks later

imaging-based PFS in cohort A. If the primary objective was reached, testing of key secondary endpoints had to be performed in a hierarchical manner: ORR in cohort A, rPFS in the overall population, time to pain progression in cohort A and OS in cohort A. Crossover to olaparib was allowed after blinding central review imaging-based progression. After analysis of 2792 samples, 778 (28%) patients were randomly assigned in a 2:1 ratio to receive olaparib at a dose of 300 mg twice daily (162 patients in cohort A, 94 patients in cohort B) or the physician's choice between enzalutamide or abiraterone (83 patients in cohort A, 48 patients in cohort B). Primary endpoint was reached and the median imaging-based PFS in the cohort A was longer in the olaparib group (7.4 months vs. 3.6 months, Hazard Ratio (HR) 0.34, 95% CI 0.25–0.47, $P < 0.001$). The ORR, assessed by blinded, independent, central review, among evaluable patients of the cohort A was 33% in the olaparib group and 2% in the control group. PFS was also longer in the overall population (cohort A and B) for the experimental group (5.8 months) compared to the control group (3.5 months), $P < 0.001$. A statistically meaningful better OS was subsequently reported for patients receiving olaparib in cohort A than those treated with NHT (19.1 months vs. 14.7 months, HR 0.69, 95% CI 0.50–0.97, $P = 0.0175$) [10]. Among patients in the control group, with imaging-based disease progression, 81% crossed over to receive olaparib, and the sensitivity analysis adjusting for the crossover showed an HR of 0.42 (95% CI 0.19–0.91). No difference was observed before or after adjustment for crossover (HR 0.96; 95% CI 0.63–1.49) for cohort B.

The PROfound study is the first trial showing an improvement in OS for mCRPC with an alteration in *BRCA1/2* or *ATM* genes, treated with PARPi, after at least the use of NHT, even if a substantial crossover was observed. In addition, olaparib significantly improved time to pain progression, a key secondary endpoint (HR 0.44; 95% CI 0.22–0.91, $P = 0.0192$), and was associated with better health-related quality of life (HRQoL) functioning over time, compared with NHT [44, 45]. These patient-reported outcomes are of importance in the setting of advanced prostate cancer. However, even if promising CRR rates were reported by TOPARP studies as well as rPFS regarding *ATM* altered patients, the inclusion in the same cohort of *ATM* and *BRCA* is questionable given function differences and marginal results in other phase III studies. A large retrospective study [46] and the CARD randomized phase III trial [47] showed that not delaying chemotherapy for eligible patients improves survival. Given these results, a standard arm allowing docetaxel may have been more appropriate. Indeed, 35% of the patients allocated to the standard arm received two consecutive NHT, but no taxane-based chemotherapy,

making the control group weaker. However, the PROfound trial was designed prior to these retrospective and CARD data [46, 47]. Other ongoing phase II studies, evaluating olaparib as maintenance therapy following chemotherapy for mCRPC, or as a single agent for localized prostate cancers, are reported in Table 1.

Niraparib

Niraparib is another PARP1/2 inhibitor with higher trapping potency and cytotoxicity than olaparib [36]. GALAHAD is an ongoing open-label phase II study evaluating niraparib in patients with mCRPC and HRR deficiency, progressing after taxane and NHT. HRR deficiency was defined as a biallelic alteration in *BRCA1/2*, *ATM*, *FANCA*, *PALB2*, *CHEK2*, *BRIP1*, or *HDAC2* assessed by a plasma or tissue-based test. Patients received 300 mg of niraparib daily. The primary endpoint was the ORR. A CRR, defined as ORR, conversion of CTC, or more than 50% decline in PSA level, was evaluated. Preliminary results were recently reported, regarding a population of 81 patients with a biallelic HRR deficiency (46 *BRCA1/2* and 35 non-*BRCA*) [48]. Of the 51 patients with a measurable disease, the ORR in the “*BRCA* group” was 41% (95% CI 23.5–61.1%) compared to 9% (95% CI 1.1–29.2%) in the “non-*BRCA* group”; and the CRR was 63% (95% CI 47.6–76.8%) compared to 17% (95% CI 6.6–33.7%), respectively. Median PFS and OS in *BRCA* were 8.2 months (95% CI 5.2–11.1 months) and 12.6 months (95% CI 9.2–15.7 months), respectively, versus 5.3 months (95% CI 1.9–5.7 months) and 14.0 months (95% CI 5.3–20.1 months) in non-*BRCA*. Grade 3 and 4 adverse events were mostly hematologic with anemia (29%), thrombocytopenia (15%) and neutropenia (7%), managed with dose reduction or interruption.

GALAHAD is a phase II study with a small number of patients. Thus, results on efficacy need to be interpreted cautiously. As for olaparib, niraparib seems to be more efficient in *BRCA*-altered patients. Efficacy is in the same order of magnitude as olaparib (ORR of 52.4% and 41% for *BRCA* groups in TOPARP-B and GALAHAD, respectively) even if we would expect a greater effect in a pure biallelic population. Toxicity was manageable and similar to olaparib.

Three other ongoing phase II studies evaluating niraparib as monotherapy are reported in Table 1. One for mCRPC and two for localized prostate cancer. To date, there is no phase III study investigating niraparib as monotherapy.

Rucaparib

Rucaparib has a cytotoxic power and trapping efficacy comparable to olaparib [37]. The TRITON-2 phase 2 trial evaluated rucaparib 600 mg twice daily in patients

with mCRPC and mono- or bi-allelic deleterious somatic or germline alteration in HRR genes (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *NBN*, *PALB2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*). Alterations were tested on plasma or tumor tissue. Patients had a progression after one or two NHT and one taxane-based chemotherapy. Primary outcomes were the ORR and the PSA response rate. One hundred and fifteen patients had a *BRCA1/2* alteration (44 germline, 71 somatic) [49]. The ORR was 43.5% (95%CI 38.1–63.4%) for the 62 ORR-evaluable patients; no differences were observed between germline and somatic mutated patients. With a median follow-up of 17.1 months, the median duration of response was not reached yet. The PSA response rate was 54.8% (95% CI 45.2–64.1%). PSA responses seemed smaller in the *BRCA1* (15.4%; 2 of 13 patients) or mono-allelic patients (11.1%; 1 of 9 patients) compared to *BRCA2* (59.8%; 61 of 102 patients) or biallelic patients (75.0%; 27 of 36 patients) (although these are small populations). Seventy-eight patients had a non-*BRCA* HRR alteration [50]. The PSA response rate was 4.1%, 6.7% and 16.7% in the *ATM* group (49 patients), *CDK12* cohort (15 patients) and *CHEK2* group (12 patients), respectively. The ORR was 10.5% in the *ATM* group (19 evaluable patients), 0% in the *CDK12* cohort (10 evaluable patients), and 11.1% in the *CHEK2* group (9 evaluable patients). Of the 14 evaluable patients with other HRR gene alterations, 4 (28.6%) had a radiographic response and 5 (35.7%) had a PSA response. Encouraging results are seen for *PALB2*, *BRIP1* and *RAD51*. Indeed, both patients with a *PALB2* alteration had PSA responses and one had a partial radiographic response. One of the 2 *BRIP1*-altered patients and a patient with an *RAD51B* alteration had radiographic and PSA responses, both ongoing [50]. Adverse events were comparable to other PARPi.

Again, these results suggest that *BRCA1/2* and *PALB2*, both effectors of HRR, are interesting targets, while *ATM*, *CDK12* and *CHEK2*, sensors of HRR, may be less directly involved. The other non-*BRCA* HRR genes warrant further investigation. This is the first phase II study comparing mono- and biallelic, somatic and germline altered patients. The results, even with small cohort of patients, raise hypotheses for further investigations suggesting better efficacy for biallelic altered patients and no differences between somatic and germline status.

The TRITON-3 study (NCT02975934) is an ongoing phase III trial comparing rucaparib *versus* abiraterone, enzalutamide or docetaxel (physician's choice) after 1 NHT but no chemotherapy, for patients with mCRPC and a deleterious mutation of *BRCA1/2* or *ATM* (Table 1).

Talazoparib

Talazoparib is the PARPi with the strongest trapping efficiency [37]. Its efficacy is 20- to 200-fold greater than the others [51]. TALAPRO-1 is an ongoing phase II trial evaluating talazoparib 1 mg daily in patients with mCRPC and mono- or bi-allelic HRR gene alterations (*CDK12* was not considered as an HRR gene). They have received at least one taxane-based chemotherapy regimen and one or more NHT. Interim results were recently reported with 113 patients having received talazoparib and 75 patients evaluable for the primary endpoint of ORR (41 *BRCA1/2*, 3 *PALB2*, 17 *ATM* and 14 patients with other HRR gene alterations) [52, 53]. In the *BRCA*, *PALB2* and the *ATM* groups, ORR was 43.9%, 33.3% and 11.8%, respectively. No response was observed in the other HRR groups. Most common adverse events were slightly more frequent than other PARPi, namely anemia (42.5%, all grades) and nausea (32.7%, all grades) [53].

With these convincing results, PARPi are becoming accepted as options to treat patients with mCRPC. *BRCA1/2* alterations are predictive of response to PARPi and are the best candidates for treatment, irrespective of somatic or germinal status. The biallelic inactivation also appears to be important, with most of the responses observed in this group. More studies are awaited to support these statements and will not only explore the PARPi efficacy earlier in the medical care (i.e., mCSPC or localized prostate cancers) but also in combination with other drugs.

Treatment combination with PARP inhibitors

Even if sustained efficacy is observed with PARPi used alone, primary and secondary resistances are seen. To try to potentiate their action, trials are underway to evaluate the use of PARPi in combination with other drugs. The main studies are summarized in Table 2.

PARP inhibitors and new hormonal therapies

In 2013, Polkinghorn et al. showed that AR regulates a transcriptional program of DNA repair genes and that NHT results in downregulation of DNA repair genes [54]. Moreover, Schiewer et al. demonstrated, using different cell lines and xenografts, that PARP-1 promotes AR functions [55]. Recently, two studies confirmed the association between AR, HRR and PARP, on cell lines and xenografts. They showed that androgen deprivation therapy (ADT) or enzalutamide could result in a state of BRCAness leading to sensitivity to PARP inhibition of prostate cancer cells [56, 57]. Based on these results Clarke et al. assessed the synergy between olaparib and abiraterone in a randomized phase II study [58]. One hundred and forty-two patients with mCRPC, who previously received docetaxel but not

Table 2 Phase II or III trials using PARP inhibitors in combination to treat prostate cancers

CTID	Treatment	Phase	No. patients or estimated enrollment	Disease status	Mandatory HRR status for inclusion	Determination method for HRD	Primary endpoints	Results
NCT01972217	Abiraterone ± olaparib	2	142	mCRPC after docetaxel, no prior NHT	No	Plasma or blood or tumor	Radiographic PFS	13.8 months (combination) versus 8.2 months (control), $P=0.034$, HR = 0.65 (CI 95% 0.44–0.97)
NCT03732820/PROpel	Abiraterone ± olaparib	3	720	mCRPC, 1st line	No	Tumor	Radiographic PFS	Ongoing, not recruiting
NCT02484404	Olaparib + durvalumab	2	17	mCRPC after 1 NHT	No	Not performed	Clinical efficacy	PSA response rate: 53%, Radiographic response: 44% Radiographic PFS: 16.1 months
NCT02861573/KEY-NOTE-365 cohort A	Olaparib + pembrolizumab	2	41	mCRPC after at least docetaxel	No	Not performed	PSA response rate, safety	PSA response rate: 13%
NCT03834519/KEY-LINK-010	Olaparib + pembrolizumab vs NHT	3	780	mCRPC after CT and 1 NHT	No	Not performed	OS, radiographic PFS	Recruiting
NCT03810105	Olaparib + durvalumab	2	32	Castration Sensitive Biochemically Recurrent nmPC	Bi- or mono-allelic deleterious HRD	Undescribed method	Number of undetectable PSA	Recruiting
NCT04336943	Olaparib + durvalumab	2	30	Castration Sensitive Biochemically Recurrent nmPC	Deleterious HRD, bi-allelic <i>CDK12</i> alteration, MSI ^a	Undescribed method	Number of undetectable PSA	Recruiting
NCT03787680/TRAP	Olaparib + ATRi (AZD6738)	2	45	mCRPC after docetaxel or 1 NHT	Cohort 1: no Cohort 2: ^a HRD	Tumor or blood	ORR in DNA repair proficient patients	Recruiting
NCT03516812	Olaparib + testosterone	2	30	mCRPC after 1 NHT, no chemotherapy	50% with ^a deleterious HRD, 50% with competent HRR	Tumor or blood	PSA decrease, AES	Recruiting
NCT02893917	Olaparib ± cediranib	2	90	mCRPC after 2 lines of treatment	No	Not performed	Radiographic PSA	Ongoing, not recruiting
NCT03748641/MAGNITUDE	Abiraterone ± niraparib	3	1000	mCRPC, 1st line	No	Tumor	Radiographic PFS	Recruiting
NCT04497844/AMPLITUDE	ADT + abiraterone ± niraparib	3	788	mCSPC	No	Tumor	Radiographic PFS	Recruiting
NCT03431350	Niraparib + cetrelimab or niraparib + abiraterone	1–2	148	mCRPC after 1 or 2 NHT	No	Not performed	ORR and AES	Recruiting
NCT04455750/CASPAR	Enzalutamide ± rucaparib	3	1002	mCRPC, 1st line	No	Tumor	Radiographic PFS and OS	Not yet recruiting
NCT03338790/Check-Mate 9KD	Nivolumab + rucaparib/enzalutamide/docetaxel	2	330	mCRPC	No	Not performed	ORR and PSA response rate	Ongoing, not recruiting

Table 2 (continued)

CTID	Treatment	Phase	No. patients or estimated enrollment	Disease status	Mandatory HRR status for inclusion	Determination method for HRD	Primary endpoints	Results
NCT03395197 (TAL-APRO-2)	Enzalutamide ± talazoparib	3	1037	mCRPC, 1st line	No	Not performed	Radiographic PFS	Recruiting
NCT04332744/ZZ-first	ADT + enzalutamide ± talazoparib	2	54	mCSPC high volume	No		PSA complete response rate	Recruiting

CRPC metastatic castration-resistant prostate cancer, *mCSPC* metastatic castration-sensitive prostate cancer, *nmPC* non-metastatic prostate cancer, *NHT* new hormonal therapy, *HRR* homologous recombination repair, *HRD* homologous repair deficiency, *CTID* clinical trial identification, *PFS* progression free survival, *ORR* objective response rate, *OS* overall survival, *PSA* response rate: decline of more than 50, *AES* adverse events. *ATRI*: ceralasertib: orally available inhibitor of ataxia telangiectasia and rad3 related (ATR) kinase

^a Mono- or bi-allelic status not specified

any NHT, were blindly randomized between abiraterone with placebo, and abiraterone with olaparib. Only 21 patients (15%) had confirmed or suspected HRR alteration (allelic status not known), 35 patients (25%) were classified as HRR wild-type, and 86 (61%) had partially characterized HRR status (HRR wild-type by plasma and/or germline test, but no valid tumor test, or no valid tumor, plasma and germline test). There was a significant improvement of rPFS in the combination arm compared to the control arm (13.8 months vs. 8.2 months, $P=0.034$). The predefined subgroup analysis for HRR-altered patients and HRR-wild type ones was not significant, probably due to the small population. Results for OS were immature by the data cut-off, and no statistically significant differences could be seen. The toxicity of the combination was high, i.e., 54% of the patients experienced grade 3 or more adverse events in the experimental arm versus 28% in the comparator arm. Seven patients (10%), aged 66–88 years old, in the combination arm had serious cardiovascular events (4 myocardial infarctions, 1 fatal cardiac failure, 1 chronic cardiac failure, 1 fatal ischemic stroke) compared with 1 thrombotic stroke in the control arm. At baseline, 62% and 56% had cardiovascular risk factors in the combination and comparator arms, respectively. Of note, median treatment duration was longer in the combination arm (338 days vs. 253 days for abiraterone in each arm, 309 days for olaparib vs. 253 days for placebo). This study shows a synergistic interaction between NHT (abiraterone) and PARPi (olaparib), even in the absence of HRR alteration, strengthening the hypothesis that NHT induce a BRCAness state in prostate cancers. However, a relatively high cardiovascular toxicity is observed (10%) in the combination arm, leading to death in almost 3% of cases. Thus, the association should be used with caution in patients with cardiovascular history.

Based on these results, the ongoing phase III trial PROpel (NCT03732820) randomizes patients with mCRPC between abiraterone with olaparib and abiraterone with placebo, as first-line treatment, irrespective of HRR status. The primary endpoint is rPFS; secondary endpoints include OS and health-related quality of life. The effect of HRR alteration will be studied in exploratory analyses.

Several ongoing studies are evaluating the association of a PARPi combined with NHT with mainly rPFS as primary endpoint. MAGNITUDE (NCT03748641) and AMPLITUDE phase III trials (NCT04497844) randomize patients with advanced prostate cancer between abiraterone or abiraterone and niraparib in castration resistance and castration sensitive setting, respectively. The CASPAR trial (NCT04455750) is investigating a combination of enzalutamide and rucaparib compared

to enzalutamide in patients with mCRPC (irrespective of HRR status). Talazoparib is being evaluated in association with enzalutamide in the TALAPRO-2 trial.

Veliparib is the PARPi with the lowest trapping activity [36] and has only been tested in combination with other treatments in mCRPC. A phase II trial aimed to assess the association of abiraterone and veliparib in patients with mCRPC irrespective of HRR status [59]. Patients were randomly assigned to receive abiraterone (arm A) or abiraterone with veliparib (300 mg twice per day, arm B). There were no statistically significant differences between the 2 arms regarding PSA response (arm A: 63.9% and arm B: 72.4%, $P=0.27$) or median PFS (arm A: 10.1 months and arm B: 11 months, $P=0.99$). To date, there is no other ongoing trial investigating veliparib in prostate cancer.

PARP inhibitors and immunotherapy

Several preclinical studies give strong rationale for using immunotherapy. Indeed, PD-L1 expression rises from localized to mCRPC [60], is higher in aggressive primary prostate cancers [61] and is more frequently expressed in dendritic cells of patients progressing under enzalutamide [62], suggesting immune escape as a progression pathway in prostate cancer. However, after a promising start and demonstration of improvements in OS in 2010 with the injection of activated autologous peripheral-blood mononuclear cells [63], the outcomes provided by immune check-point inhibitors remain mixed [64–66].

A recent study has shown that PARPi could act as immunomodulatory agents in DDR-mutated cells [67]. PARPi induce accumulation of cytosolic DNA fragments, that activate the cGAS/STING pathway, stimulating the innate immune system through an interferon-mediated response. Interferon (IFN) induces PD-L1 expression, limiting the cytotoxic immune response, which could be overcome by PD-L1 blockade. Recently, the phase II KEYNOTE-199 study, investigating pembrolizumab in patients with mCRPC refractory to docetaxel, showed that DDR deficiency could be a marker for response to immunotherapy [66]: over the 9 patients with a response and a tumor sample, 6 had an evaluable whole-exome sequencing data. Out of these 6 patients, 4 had a DDR gene alteration (1 multiple alteration including *BRCA2*, *FANCA*, and *RAD54* alterations; 2 with *TP53* alteration, and 1 with a *BRCA2* alteration).

Based on these results, several studies combining immunotherapy and PARPi are ongoing. The first phase II study to be published included 17 patients with mCRPC that had progressed after previous NHT, irrespective of HRR status treated by durvalumab and olaparib [68]. Nine patients (53%) had a PSA decline of more than 50%, and over the 13 RECIST-evaluable

patients, 4 (30.8%) had an objective response. Of the nine patients with a PSA decline, 6 had a biallelic *BRCA2* alteration. The PSA response rate was 100% (6/6) in case of a biallelic *BRCA2* alteration compared to 27% (3/11) in the absence of a biallelic HRR alteration. Three of the 8 non-responder patients had a monoallelic *BRCA2* shallow deletion, and one had a shallow deletion of *BRCA2*, combined with a variant of uncertain significance of *BRCA2*. Grade 3–4 adverse events were comparable to the previous PARPi studies (i.e., anemia 24%, lymphopenia 12% and nausea 12%). Four patients had immune-related adverse events manageable with corticosteroids. Even if PARP inhibition was shown to increase PD-L1 expression, particularly in *BRCA2* depleted cells [69], the cohort of this preliminary study suggests that most of the efficacy is seen in the *BRCA2*-altered population and therefore may only come from olaparib with no advantage of the addition of durvalumab.

More recently, preliminary results from the phase Ib/II KEYNOTE-365 study were reported: 41 patients with heavily pretreated mCRPC (irrespective of DDR alterations) were included in cohort A, to receive olaparib and pembrolizumab at usual doses [70]. None of the patients had HRR genes alteration. The composite response rate (radiographic, or PSA or CTC response) was 15%. Twenty-one patients (51%) experienced grade 3 or more adverse events (mostly anemia, nausea and fatigue). The CRR of this study was low. It was the same as for patients without HRR alterations in the TOPARP-A study (6%), but with higher toxicity [39]. However, longer follow-up is needed.

The ongoing KEYLINK-010 study (NCT03834519) is the only phase III trial combining immunotherapy and PARPi in patients with mCRPC (unselected for HRR gene alterations), previously treated with docetaxel and one NHT. Patients are randomly assigned to receive pembrolizumab with olaparib, or investigator's choice of NHT (abiraterone or enzalutamide, according to previous NHT).

Early results of the association of olaparib with immunotherapy are mixed. With variable toxicities, the additive or synergistic effects of such a combination, especially in HRR-altered patients, remain unclear. However, results presented are preliminary with a median follow-up under one year, as it is known that some patients can respond for a long time, as observed in a phase III clinical trial using ipilimumab [71]. Results with a larger phase III population and a longer follow-up will help us to explore the association. Other ongoing phase II trials combining immunotherapy with olaparib, niraparib or rucaparib are listed in Table 2.

Other combinations

Chemotherapies are tested as combination partners for PARPi. The most frequently used chemotherapies are DNA-damaging agents, such as platinum or other alkylating agents to enhance dependency on PARP enzymes, or topoisomerase inhibitors to freeze the fork and increase trapping cytotoxicity [72]. Early promising efficacy has been seen in ovarian cancers with, in return, a higher toxicity [73]. Since then, most PARPi are developed as maintenance therapies after chemotherapy. To date, the efficacy of the veliparib–temozolomide combination is the only one reported and it showed modest activity [74]. Other trials are awaited to better explore these combinations (Table 1).

Several preclinical studies have shown that the association of PARPi with other DDR inhibitors, such as ataxia telangiectasia and rad3-related kinase (ATR) inhibitors, could resensitize PARP-resistant cells or xenografts [75, 76]. Indeed, *BRCA*-deficient tumors which are resistant to PARPi seem to have an increased dependency for the ATR pathway for fork stabilization. Thus, the combination of PARPi to ATR inhibitors, unprotecting the stalled fork, may overcome the PARPi resistance and restore the synthetic lethality. The ongoing phase II study TRAP (NCT03787680) assesses the efficacy of a PARPi (olaparib) and an ATR inhibitor (AZD6738).

Based on these strong rationale, NHT, immunomodulatory agents, chemotherapies, DDR agents or other targeted therapies could free PARPi from HRR alteration dependency and enhance their efficacy. However, physicians must be aware of the potential higher toxicities.

Biomarkers of response to PARP inhibitors

As mentioned before, not all HRR alterations have the same impact on PARPi efficacy. The TOPARP-B trial showed good CRR and ORR for *BRCA1/2* and *PALB2* altered-patients (83.3% and 52.4%, respectively, for *BRCA1/2*; 57.1% and 33.3% for *PALB2*), while almost no RECIST or biological responses were observed in *ATM* or *CDK12* altered-patients [40]. The PROfound trial confirmed these results and showed an OS improvement only in the *BRCA/ATM* group, however within this cohort *ATM* alterations did not show the same magnitude of efficacy neither in rPFS, nor in OS [10]. The same results were observed for niraparib, with an ORR of 41% in the *BRCA* group compared to 9% in the non-*BRCA* group (GALAHAD trial) [48]. TRITON-2 showed an ORR of 43.5% in the *BRCA* group, and long-lasting response for *BRIP1* and *RAD51* mutated-patients. But almost no response was observed for *ATM*, *CHEK2* or *CDK12*. Moreover, the ORR was lower for mono-allelic alterations (11.1%) compared to bi-allelic alterations (75.0%) [49, 50]. No differences were observed between

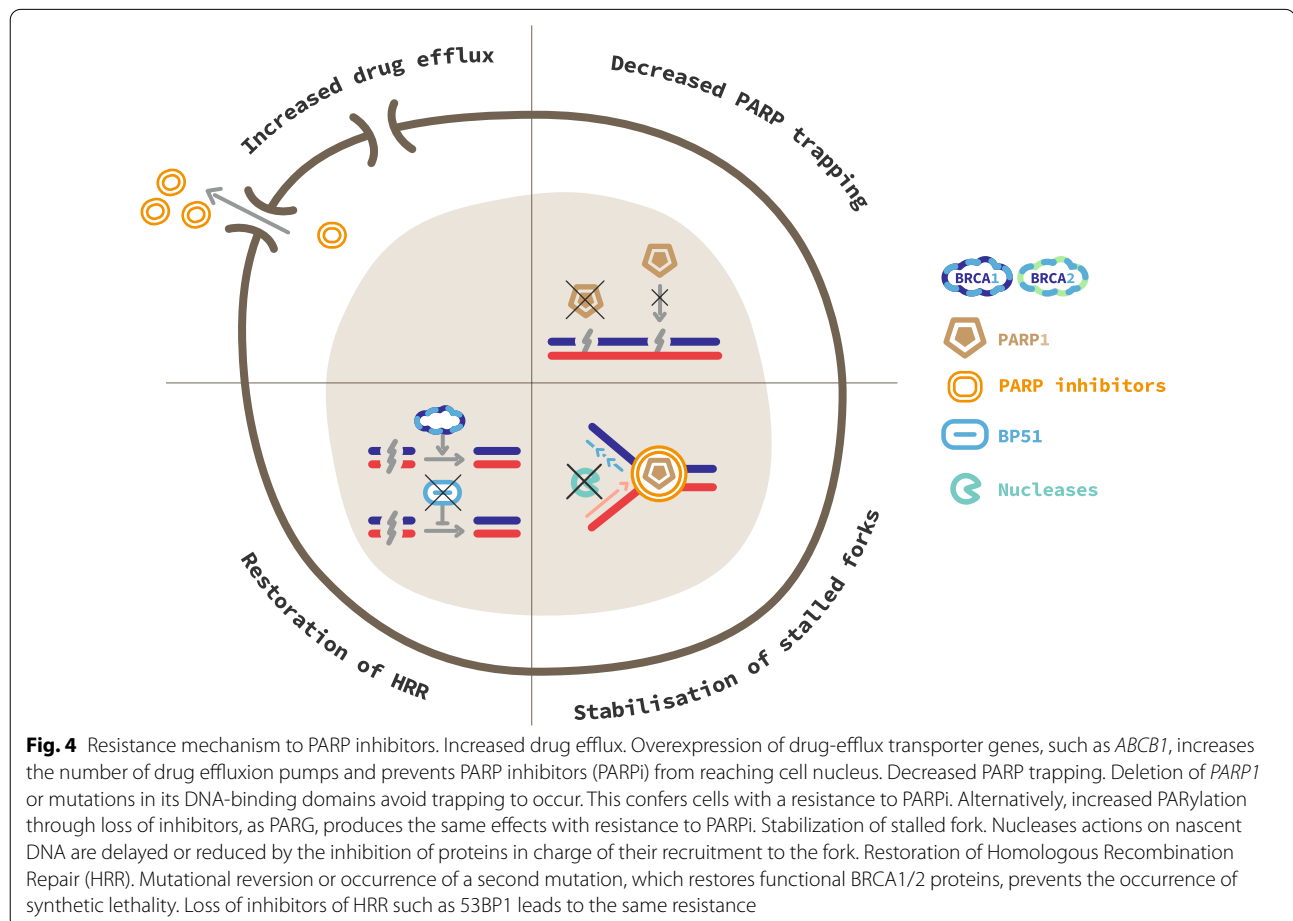
somatic and germline *BRCA1/2* mutations [49]. TAL-APRO-1 showed a good ORR in the BRCA group and no, or few, responses for other HRR genes [52]. Finally, it is noteworthy that within the BRCA group, a recent study reported better outcomes in patients with *BRCA2* compared to *BRCA1* mutations, with no differences in terms of allelic fraction or germinal versus somatic mutations. This small retrospective study remains hypothesis-generating with, as expected, 10 times more *BRCA2* than *BRCA1* alterations [77].

Overall, these data suggest that HRR effectors, mainly *BRCA* alterations, are better than sensors of DSB for predicting PARPi efficacy (Fig. 1).

Resistance mechanisms (Fig. 4)

PARPi resistance mechanisms (Fig. 4) are due to clonal selection following diverse genetic events that alter synthetic lethality. First cells can regain HRR capacity through mutational reversion of *BRCA1/BRCA2* or even more frequently due to secondary mutations that restore the open reading frame of those genes [78]. Loss of functional antagonists of *BRCA1* can also restore HRR. For

instance, the loss of the P53BP1 expression in *BRCA1* deficient cells specifically rescues HRR [79]. *BRCA2* reversion mutations were reported on cell-free DNA in progressive patients with mCRPC treated by olaparib or talazoparib [80]. Second, the drug intracellular uptake can be reduced through up-regulation of P-glycoprotein efflux pump genes (*ABCB1*) [81]. Third, mutations of *PARP1* preventing trapping can lead to PARPi resistance, highlighting the importance of trapping in PARPi lethality [82]. Forth, loss of proteins (e.g., TET2, EZH2, PTIP, SLFN11, SMARCL1) involved directly or indirectly in the recruitment of nucleases onto unprotected *BRCA1/2* deficient replicational forks can also lead to PARPi resistance. Those data highlight that PARPi cytotoxicity in *BRCA2*- or *BRCA1*-deficient cells is also due to nuclease action on stalled replication forks by PARP [83, 84]. Finally, the microenvironment may also play a role in PARPi resistance. It has been shown that the expression of transforming growth factor beta receptor (TGF β R) kinase on malignant cells, which is activated by bone marrow stromal cells-derived transforming growth factor beta 1 (TGF- β 1), could enhance the DSB repair system in



leukemia cells [85]. Since bone metastases are predominant in prostate cancers it may be interesting to investigate this hypothesis, especially in *BRCA*-altered patients. Thus, a better understanding and monitoring of such resistances using liquid biopsies may guide subsequent treatments including combination of PARPi with other agents (e.g., epigenetic treatments, TGF β inhibitors).

PARP inhibitors compared

As seen before, four PARPi are in development for mCRPC: olaparib, niraparib, rucaparib and talazoparib. Talazoparib has the strongest trapping efficiency, and its cytotoxic efficacy is 20- to 200-fold better than the others [36, 37]. However, with olaparib, it is less selective for PARP-1 than rucaparib or niraparib [86]. Regarding efficacy as a monotherapy, the ORR between the four PARPi is roughly similar, between 40 and 50% for *BRCA*-altered patients in the four phase II studies published to date [40, 48, 49, 52]. Toxicity is also equivalent between the four molecules, mostly cytopenia, nausea and fatigue. Surprisingly, 11 patients (4%) in the olaparib group compared to 1 (1%) in the control group, experienced a pulmonary embolism in the PROfound trial [43]. This adverse event was not described in the other major studies with olaparib [7, 8, 87]. The clinical significance of the occurrence of these cases is difficult to interpret and might be due to the type of cancer or the association with ADT. Of note, all grades blood creatinine increases were seen in 10 to 15% of patients treated with olaparib, rucaparib and niraparib but not with talazoparib. This is due to the inhibition of renal transporters (MATE-1 and MATE2-K) which are involved in active secretion of creatinine for olaparib and rucaparib, and probably to hemodynamic impairment for niraparib. In most cases, there is no direct impact on renal function, and the issue is resolved with dose holds [88–90]. Regarding drug interactions, olaparib and rucaparib are metabolized by CYP450 and inducers or inhibitors of the enzymes should be avoided, while talazoparib and niraparib do not have major drug-drug interactions (accessdata.fda.gov). This last point, particularly relevant in an often older population with a substantial polypharmacy, is known to be the weakness of some NHT. The number of tablets taken daily can also be of importance, regarding observance or swallowing problems, and it ranges from one tablet for talazoparib, to 3 tablets once a day for niraparib, or 2 tablets twice a day for rucaparib and olaparib.

The evidence discussed above should be taken into account cautiously, since no direct comparisons between different PARPi have been done within one clinical trial. Perhaps, the patient's profile as well as the development of these drugs in different indications or with different combinations will help physicians to make their choice.

Molecular profiling, potential and limits

The use of molecular profiling is becoming increasingly prevalent in oncology. Up to now it was performed essentially on tissue samples. Mateo et al. profiled 470 treatment-naïve prostate biopsies, of which 61 patients also had biopsies at castrate-resistant stage [91]. The median time between the two same-patient biopsies was 45.2 months (12–211 months). An increase in AR mutations and amplifications was found, as well as increased *TP53*, *RB1* and *PI3K/AKT* pathway alterations in mCRPC, suggesting that they could emerge with treatment selection pressure. Conversely aberrations in HRR pathways (seen in 9 of the 61 patients) were stable between metastatic and primary biopsies, in line with previously published data [92]. The limited number of HRR-altered patients prevents from making broad conclusions, but repeating biopsies to look for late acquisition of HRR alterations may be irrelevant.

However, tissue biopsies are of insufficient quality for molecular analyses in a non-negligible quota of patients. Thus, 31% of biopsies failed molecular testing in the PROfound trial and complementary techniques are needed in order to increase the chance of screening [43]. In this last trial, plasma-derived circulating tumor DNA (ctDNA) from patients was collected as part of the screening process and was prospectively analyzed at Foundation Medicine, Inc (FMI) using the FoundationOne Liquid CDx assay. Eighty-one percent (503/619) of ctDNA samples tested yielded a result. High concordance between tumor tissues and ctDNA was found, with 81% positive percentage agreement and 92% negative percentage agreement [93]. Of the 181 patients in the *BRCA/ATM* cohort of the study who consented and provided a plasma sample for ctDNA testing, 42 (23.2%) samples failed analyses. *BRCA/ATM* alterations were identified in 111/139 patients (79.9%). The rPFS [HR=0.33 (95% CI 0.21–0.53)] improvement was in the same order of magnitude as the one in the Intention to Treat population identified by tumor tissue testing [HR=0.34 (95% CI 0.25–0.47)] [94]. Thus, ctDNA could offer additional opportunities to patients who are not eligible for tumor tissue testing. However, not all patients have concordant results and it can be tough to estimate allelic fraction. Indeed, it depends on tumor cell percentage, clonality and ploidy of the tumor sample. To enhance efficiency, ctDNA analyses should be done before the introduction of new treatment, when the disease is progressing, especially since ctDNA availability reduces right after the initiation of an effective treatment, such as ADT [95]. The optimal approach for biomarkers should combine, if possible, tissue and liquid biopsies as they can be complementary.

PARP inhibitors in 2021: Where are we? What will be the future challenges?

PARP inhibitors are paving the way of precision medicine in prostate cancer, followed by drugs targeting the PI3k AKT mTOR pathway. While roughly one quarter of patients with mCRPC harbor somatic or genetic HRR gene mutations, not all derive benefit from PARPi. Olaparib obtained FDA approval at a dose of 300 mg twice daily on all genes tested (except *PP2R2A*), based on the first results of the PROfound trial with improvement on rPFS. However, given the benefit in OS for cohort A, EMEA approval has just been formalized, and restricted to *BRCA1/2* regardless of the somatic or germinal status (*ATM* was excluded). The benefit in OS for cohort A may be nuanced by a “weak” standard arm (i.e., no chemotherapy and half of patients with 2 back-to-back NHT as first lines for mCRPC). The PROfound trial has been designed before the results of the CARD study which highlighted the necessity for eligible patients not to delay chemotherapy in order to maintain a survival benefit [47]. Results of the TRITON-3 trial (NCT02975934; Table 1) which incorporates docetaxel in the standard arm will be of interest. It is noteworthy that results of the TOPARP-B trial suggest a better ORR but with higher toxicity using 400 mg twice daily compared to 300 mg twice daily [40]. That said, these data might be interesting for dosing patients with good tolerance and absence of response. Olaparib also improved time to pain progression and HRQoL, strengthening its clinical impact [44, 45]. These patient-reported outcomes are taken into consideration for EMEA and FDA approvals in the setting of mCRPC. Treatment with PARPi used alone is based on a screening of genes, with questions regarding the panel of genes to test, accessibility, cost and the population who may benefit from such a test. While HRR-mutated genes seem to occur early, with a suggested low enrichment from localized to metastatic disease [91, 92], the feasibility of large screening programs with archived biopsy samples may be challenging, as well as new biopsies on osteoblastic bone metastases, which are the only lesions accessible for roughly half of patients with mCRPC. For instance, in the PROfound trial screening, 30% of biopsies were not suitable for DNA analysis [96]. High concordance between tumor tissues and ctDNA was found, with 81% positive percentage agreement and 92% negative percentage agreement [93]. Liquid biopsies may then be helpful. However, some limitations regarding the determination of the allelic fraction results can be seen. Detection of somatic HRR-mutated genes first may be more efficient, since they are two times as frequent as germinal mutations. Nevertheless, in cases of somatic mutation, a germinal mutation must be sought for genetic counseling. Issues related to patient consent to involve their family in

their research of genetic patrimony may be challenging and raise ethical considerations. It is then of importance in each country, to think about a specific patient's pathway related to a biomarker-based approach (depending on biopsies suitable for analysis), and potentially involving genetic counseling. Allelic distribution seems to be important to better predict efficacy of PARPi, since only a biallelic silencing is associated with loss of function of tumor suppressor genes. However, to date its real impact in daily clinical practice is still unknown despite promising results for ORR [48, 49]. Prospective and retrospective studies investigating HRR status [33, 96] in patients with mCRPC, showed co-occurrence between 2 or more genes involved (mostly with *BRCA2*, *CDK12* and *ATM*) in this pathway, raising questions about biological impact on HRR and their predictive nature. Combination studies using PARPi with either NHT or immune checkpoint inhibitors based on robust rationale are still under evaluation with ongoing phase III trials. While benefits may be maintained regardless of HRR status, major toxicities have to be prevented in combination with NHT. Finally, platinum may be efficient in this setting since they induce intra-stand cross-links repairs using NER and HRR systems. A recent real-world cohort study investigating carboplatin and olaparib in patients with mCRPC and mutations in either *BRCA1*, *BRCA2* and *ATM* did not find any differences in PFS between the 2 drugs [97]. While PARPi is indicated according to platinum sensitivity in ovarian and pancreatic cancers, data in prostate cancer need further investigation to better delineate the role of platinum, with potential leads following resistance to PARPi (NCT04288687, PLATI-PARP trial).

Conclusions

Prostate cancer is the first disease where overall survival has been improved using a PARP inhibitor. Up until now, similarly to ovarian cancers [7], somatic and/or germinal *BRCA 1* and *2* aberrations seem to be the most predictive biomarkers of efficacy of PARPi. Data regarding the other HRR genes are generating hypotheses for further studies, though some challenges must still be overcome regarding the screening of these patients, for instance involving genetic counseling. Results of other ongoing phase III trials assessing the efficacy of a PARPi used alone or in combination are awaited, to better define their place with regard to standard treatments and platinum-based chemotherapies.

Abbreviations

ADT: Androgen deprivation therapy; AR: Androgen receptor; ATR: Ataxia telangiectasia and rad3-related kinase; BER: Base excision repair; CRR: Composite response rate; CSS: Cause-specific survival; CTC: Circulating tumor cell; ctDNA: Circulating tumor DNA; DDR: DNA-damage response; FANC: Fanconi Anemia; FMI: Foundation Medicine, Inc; HR: Hazard ratio; HRD: Homologous

recombination deficient; HRQoL: Health-related quality of life; HRR: Homologous recombination repair; IFN: Interferon; LOH: Loss of heterozygosity; mCRPC: Metastatic castration-resistant prostate cancer; MMEJ: Microhomology-mediated end joining; MMR: Mismatch repair; NAD⁺: Nicotinamide adenine dinucleotide; NER: Nucleotide excision repair; NGS: Next-generation sequencing; NHEJ: Non-homologous end joining; NHT: New-hormonal therapy; ORR: Objective response rate; OS: Overall survival; PARP: Poly(adenosine diphosphate-ribose) polymerase; PARPi: Poly(adenosine diphosphate-ribose) polymerase inhibitor; PFS: Progression-free survival; RECIST: Response evaluation criteria in solid tumors; rPFS: Radiographic progression-free survival; SSB: Single-strand break; TGF- β 1: Transforming growth factor beta 1; TGF β R: Transforming growth factor beta receptor.

Acknowledgements

The authors thank Pippa McKelvie-Sebileau for providing medical writing support and Nelly Rivière for the figures.

Authors' contributions

HM collected and analyzed data regarding biology of the DDR pathway and action or resistance mechanisms of PARP inhibitors. DT reviewed the literature regarding prostate cancers and PARP inhibitors. He wrote most of the article and designed the work. GR have drafted the work and wrote the discussions and conclusions. He substantively revised the article. MC, MA, NV, IS, PS and NS revised the work with caution and gave their expert opinion. All authors read and approved the final manuscript.

Funding

The authors declare that they did not receive funding for this work.

Availability of data and materials

Not applicable.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 14 December 2020 Accepted: 10 March 2021

Published online: 29 March 2021

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NIT: 800.176.089-2

COMPROBANTE DE RECAUDO SISTEMA SIPI

Radicado: NC2019/0011591
Recibo: 22-69496
Fecha: 05/08/2022

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TERAPIA DE COMBINACIÓN PARA CÁNCER DE PRÓSTATA

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1	50005-01-03	Modificaciones / Correcciones al registro Patente PCT (DESCUENTO INTERNET)	1	\$ 176,000	\$ 176,000
TOTAL					\$ 176,000