Genomic Biomarkers and Genome-Wide Loss-of-Heterozygosity Scores in Metastatic Prostate Cancer Following Progression on Androgen-Targeting Therapies

Amado J. Zurita, MD1; Ryon P. Graf, PhD2; Guillermo Villacampa, PhD3; Kira Raskina, MD1; Ethan Sokol, PhD2; Dexter Jin, PhD2; Emmanuel S. Antonarakis, MD4; Gerald Li, PhD2; Richard S. P. Huang, MD2; Irene Casanova-Salas, PhD1; Ana Vivancos, PhD1; Joan Carles, MD, PhD5; Jeffrey S. Ross, MD, PhD2; Alexia B. Schrock, PhD2; Geoffrey R. Oxnard, MD2; and Joaquin Mateo, MD, PhD3

PURPOSE To study the impact of standard-of-care hormonal therapies on metastatic prostate cancer (mPC) clinical genomic profiles in real-world practice, with a focus on homologous recombination-repair (HRR) genes.

PATIENTS AND METHODS Targeted next-generation sequencing of 1,302 patients with mPC was pursued using the FoundationOne or FoundationOne CDx assays. Longitudinal clinical data for correlative analysis were curated via technology-enabled abstraction of electronic health records. Genomic biomarkers, including individual gene aberrations and genome-wide loss-of-heterozygosity (gLOH) scores, were compared according to biopsy location and time of sample acquisition (androgen deprivation therapy [ADT]-naïve, ADT-progression and post-ADT, and novel hormonal therapies [NHT]-progression), using chi-square and Wilcoxon rank-sum tests. Multivariable analysis used linear regression. False-discovery rate of 0.05 was applied to account for multiple comparisons.

RESULTS Eight hundred forty (65%), 132 (10%), and 330 (25%) biopsies were ADT-naïve, ADT-progression, and NHT-progression, respectively. Later-stage samples were enriched for AR, MYC, TP53, PTEN, and RB1 aberrations (all adjusted P values < .05), but prevalence of HRR-related BRCA2, ATM, and CDK12 aberrations remained stable. Primary and metastatic ADT-naïve biopsies presented similar prevalence of TP53 (36% v 31%) and BRCA2 (8% v 7%) aberrations; 81% of ADT-naïve BRCA2-mutated samples presented BRCA2 biallelic loss. Higher gLOH scores were independently associated with HRR genes (BRCA2, PALB2, and FANCA), TP53, and RB1 aberrations, and with prior exposure to hormonal therapies in multivariable analysis.

CONCLUSION Prevalence of HRR-gene aberrations remains stable along mPC progression, supporting the use of diagnostic biopsies to guide poly (ADP-ribose) polymerase inhibitor treatment in metastatic castration-resistant prostate cancer. gLOH scores increase with emerging resistance to hormonal therapies, independently of individual HRR gene mutations.

JCO Precis Oncol 6:e2200195. © 2022 by American Society of Clinical Oncology

INTRODUCTION Metastatic prostate cancer (mPC) is a lethal disease with pronounced genomic heterogeneity between patients.1,4 The recent approval of poly (ADP-ribose) polymerase (PARP) inhibitors5-7 for mPC with mutations in homologous-recombination repair (HRR) genes, together with other genomic aberrations showing potential value to guide treatment decisions,8-13 has accelerated the incorporation of genomic testing into clinical practice, and guidelines now recommend offering tumor genomic profiling to patients with mPC.12-14 The inclusion of genomic biomarkers into mPC clinical management is still challenged by inequalities in access to testing and unresolved questions about optimal sources of tumor material. Also, the impact of tumor evolution and therapy-induced selective pressure on clinically relevant biomarkers is not well established.11,15-17 A key question is whether biopsies collected at the time of diagnosis can inform biomarker-driven clinical decisions at later stages, after resistance to androgen deprivation (ADT) and novel hormonal therapies (NHT). Obtaining repeated metastatic biopsies to capture the evolving genomic landscape is often unfeasible, especially outside academic centers. Indeed, most of the evidence endorsing the adoption of molecular profiling has been generated from rigorously selected patient populations...
Our data support the use of archival, untreated diagnostic prostate cancer samples for next-generation sequencing testing in clinical practice toward identification of patients with HRR defects for poly (ADP-ribose) polymerase inhibitor therapy indication. Other precision medicine strategies driven by biomarkers such as AR, TP53, or RB1 may be in need of contemporaneous samples for accurate patient stratification.

**CONTEXT**

**Key Objective**
To study how prostate cancer genomic profiles change upon drug resistance, and particularly to study the impact of genomic evolution in the identification of candidates for poly (ADP-ribose) polymerase inhibitor treatment using a clinical next-generation sequencing assay.

**Knowledge Generated**
The prevalence of homologous recombination-repair (HRR) gene alterations is stable across different disease states, before/after hormonal therapy. Contrarily, biomarkers such as AR and MYC amplifications, or TP53 and RB1 loss are enriched after hormone therapy resistance. We observed that genome-wide loss-of-heterozygosity, a marker of genomic instability, independently associates with the presence of HRR gene alterations, TP53/RB1 loss and resistance to hormonal therapies.

**Relevance**
Our data support the use of archival, untreated diagnostic prostate cancer samples for next-generation sequencing testing in clinical practice toward identification of patients with HRR defects for poly (ADP-ribose) polymerase inhibitor therapy indication. Other precision medicine strategies driven by biomarkers such as AR, TP53, or RB1 may be in need of contemporaneous samples for accurate patient stratification.

from a relatively small number of academic institutions. Data from more diverse, real-world, patient sets would facilitate the delivery of precision medicine to patients with prostate cancer.

The use of PARP inhibitors for mPC with selected HRR gene mutations such as BRCA1/2 represents a prime example of molecularly guided mPC management. However, clinical outcomes of patients with different tumor HRR-associated gene mutations, and even among those with mutations in the same gene, are heterogeneous; thus, there is a need to refine biomarkers of HRR deficiency beyond individual gene mutations. One candidate biomarker is the fraction of the genome affected by loss-of-heterozygosity (gLOH), a measure of how much of the genome is affected by irreversible loss-of-allele events, reflective of genomic instability. BRCA1/2 mutations exhibit higher gLOH scores in different cancer types, and high gLOH scores associate with PARP inhibitor sensitivity in ovarian cancer. Yet, gLOH levels are lower overall in prostate cancer compared with ovarian cancer, even in BRCA1/2 defective tumors. Hence, independent evaluation of gLOH in prostate cancer should be pursued.

In this study, we leverage correlative clinicogenic data from a large cohort of patients with mPC who underwent tumor genomic profiling as part of routine clinical care, mostly in community clinics. We hypothesized that the prevalence of BRCA2 and other HRR-gene aberrations would be similar, independently of prior androgen-targeted treatment exposure or sampled disease site (primary or metastatic). We also aimed to analyze clinicogenic variables in relation to gLOH scores in early versus later stages of lethal prostate cancer progression.

**PATIENTS AND METHODS**

**Study Population**
All patients with confirmed metastatic (de novo or recurrent) and/or castration-resistant prostate cancer presentation included in the US-wide Flatiron Health-Foundation Medicine deidentified real-world clinicogenic database between January 2011 and April 2021, with available genomic profiling data on primary or metastatic tumor tissue specimens. All tissue samples were obtained between March 2002 and December 2020. Specimens were sequenced from November 2013 to December 2020. Follow-up clinical data were collected until April 2021.

**Next-Generation Sequencing**
A hybrid capture-based next-generation sequencing (NGS) assay was performed on tumor tissue biopsies in a Clinical Laboratory Improvement Amendments–certified laboratory and College of American Pathologists–accredited laboratory (Foundation Medicine, Cambridge, MA). FoundationOne or FoundationOne CDx assays interrogated exons from 315 to 324 cancer-related genes (depending on panel version), plus select introns from at least 28 genes frequently rearranged in cancer. At least 50 ng of DNA per specimen was isolated and sequenced to high, uniform coverage (mean, > 600x) as previously described. Samples were evaluated for aberrations including single-nucleotide substitutions, indels (short variants, denoted as sv), copy-number alterations (amplifications or homozygous deletions, denoted as amp or as del), and other select gene fusions/rearrangements. Only deep deletions, those modeled to translate homozygous deletions taking into consideration sample purity and ploidy, were reported; shallow deletions, predicted to translate single copy losses,
were only considered toward calling zygosity of mutations. Amplifications were defined as ≥ 6 copies. For tumor suppressor genes, all mutations predicted to result in truncation (frameshift mutations, canonical splice-site alterations, and nonsense mutations), rearrangements, or deep deletions were considered pathogenic, together with selected known pathogenic missense mutations. For HRR-related tumor suppressor genes, prediction of zygosity status and biallelic gene loss was calculated as described in prior studies.21

Genomic aberrations per gene, and per pathway, were annotated for each patient (Data Supplement). Tumor mutational burden was determined on 1.1 Mb of sequenced DNA.26 gLOH was defined as the percentage of the genome demonstrating loss-of-heterozygosity using previously validated pipelines and excluding whole-arm and whole-chromosome events.26 gLOH assessment was pursued in those samples passing copy-number alteration–based quality-control metrics (signal to noise ratio) and tumor purity ≤ 30%.

**Clinical Data, Patient Eligibility, and Classification**

Deidentified baseline and longitudinal follow-up clinical data from patients treated at approximately 280 cancer clinics (approximately 800 sites of care) in the United States were retrospectively captured from electronic health records, comprising patient-level structured and unstructured data, using technology-enabled abstraction of clinical notes and radiology/pathology reports. Clinical data captured included demographics, disease extent, therapy exposure (with start and stop dates for each therapy line), and survival outcomes. Clinical data were linked to genomics data by deidentified, deterministic matching.

Cases were classified into one of three categories, on the basis of the clinical state at the time when the tumor biopsy used for genomic profiling was acquired: (1) ADT-naïve: tumor biopsy or radical prostatectomy specimens collected before ADT exposure; (2) ADT-progression/CRPC: tumor specimen obtained within 90 days before or 30 days after diagnosis of CRPC per clinical notes, with no prior exposure to NHT; and (3) NHT-progression (NHT-CRPC): tumor specimen collected after progression to treatment with NHT in the CRPC setting. To minimize confounders, we discarded any sample obtained within 30 days of initiating NHT (Data Supplement).

**Objectives and Statistical Analysis Plan**

The primary objective was to compare the prevalence of clinically relevant genomic biomarkers in primary and metastatic tissue biopsies across the mPC spectrum and therapy exposure, with emphasis on HRR-associated genes. The secondary objective was to examine clinical and genomic variables associated with gLOH scores. Overall survival was calculated from start of systemic treatment to death from any cause. gLOH was assessed as a continuous variable (percentage of the genome affected), as prior studies demonstrated that the distribution of gLOH scores in prostate cancer differs significantly from other tumor types in which dichotomic thresholds were defined.20

Chi-square tests and Wilcoxon rank sum tests were used to assess differences between groups of categorical and continuous variables, respectively. Adjustment for multiple testing with a false-discovery rate at 0.05 (Benjamini and Hochberg method) was performed. For the secondary objective related to gLOH scores, we first pursued a univariable linear regression. Next, we pursued a multivariable analysis for those biomarkers with > 5 events in the study population using a least absolute shrinkage and selection operator (LASSO) regression27 to exclude those gene alterations with a null impact in the model. Time to event end points was assessed using the Kaplan-Meier method and the log-rank test. Cox proportional-hazard models were used to obtain hazard ratios with 95% CIs. We relaxed the linearity assumption for gLOH using restricted cubic splines using the rms R package. The threshold for significance was set at 0.05 (two-sided) after adjustment. R v3.6.3 software program was used for all analyses.

This study was conducted according to the ethical principles for medical research described in the Declaration of Helsinki. Institutional review board approval of the study protocol and this analysis was obtained before study conduct and included a waiver of informed consent.

**RESULTS**

**Sample and Patient Characteristics**

We identified 1,847 cases with confirmed mPC who had been entered in the clinicogenomics integrated database between 2011 and 2021. After clinical data curation, 1,302 cases with follow-up clinical and treatment data available were retained for this analysis. Of those, genomic profiling had been pursued in tissue samples acquired either before any systemic therapy (ADT-naïve group, n = 840, 65%), after development of castration-resistance but before any NHT exposure (ADT-progression or CRPC group, n = 132, 10%), or after exposure to ≥ 1 NHT (NHT-CRPC group, n = 330, 25%; Fig 1). Five hundred seventeen (40%) cases were sequenced using the FoundationOne panel, and 785 (60%) using the later FoundationOne CDx panel. The median sequencing depth was 794× (interquartile range [IQR], 648-895), with no significant differences among samples in each of the three groups (median depth of 787×, 807×, and 805× for the ADT-naïve, ADT-progression, and NHT-exposed, respectively; see the Data Supplement for tumor content details).

The majority of samples in the ADT-naïve group were prostate primary tumor biopsies or radical prostatectomy specimens (674/840, 80%, v.20% of lymph nodes or other metastatic site biopsies), whereas in the post-NHT groups, biopsies were predominantly from lymph nodes (28%), liver (25%), or bone (16%) metastases, representing usual patterns of biopsy acquisition in real-world clinical practice. Patient and sample characteristics, as well as prior history

---

1. JCO Precision Oncology 3
2. gLOH assessment was previously validated pipelines and excluding whole-arm mutational burden was determined on 1.1 Mb of sequenced DNA.26 gLOH was defined as the percentage of the genome demonstrating loss-of-heterozygosity using previously validated pipelines and excluding whole-arm and whole-chromosome events.26 gLOH assessment was pursued in those samples passing copy-number alteration–based quality-control metrics (signal to noise ratio) and tumor purity ≤ 30%.
3. Clinical Data, Patient Eligibility, and Classification
4. Deidentified baseline and longitudinal follow-up clinical data from patients treated at approximately 280 cancer clinics (approximately 800 sites of care) in the United States were retrospectively captured from electronic health records, comprising patient-level structured and unstructured data, using technology-enabled abstraction of clinical notes and radiology/pathology reports. Clinical data captured included demographics, disease extent, therapy exposure (with start and stop dates for each therapy line), and survival outcomes. Clinical data were linked to genomics data by deidentified, deterministic matching.
5. Cases were classified into one of three categories, on the basis of the clinical state at the time when the tumor biopsy used for genomic profiling was acquired: (1) ADT-naïve: tumor biopsy or radical prostatectomy specimens collected before ADT exposure; (2) ADT-progression/CRPC: tumor specimen obtained within 90 days before or 30 days after diagnosis of CRPC per clinical notes, with no prior exposure to NHT; and (3) NHT-progression (NHT-CRPC): tumor specimen collected after progression to treatment with NHT in the CRPC setting. To minimize confounders, we discarded any sample obtained within 30 days of initiating NHT (Data Supplement).
6. Objectives and Statistical Analysis Plan
7. The primary objective was to compare the prevalence of clinically relevant genomic biomarkers in primary and metastatic tissue biopsies across the mPC spectrum and therapy exposure, with emphasis on HRR-associated genes. The secondary objective was to examine clinical and genomic variables associated with gLOH scores. Overall survival was calculated from start of systemic treatment to death from any cause. gLOH was assessed as a continuous variable (percentage of the genome affected), as prior studies demonstrated that the distribution of gLOH scores in prostate cancer differs significantly from other tumor types in which dichotomic thresholds were defined.20
8. Chi-square tests and Wilcoxon rank sum tests were used to assess differences between groups of categorical and continuous variables, respectively. Adjustment for multiple testing with a false-discovery rate at 0.05 (Benjamini and Hochberg method) was performed. For the secondary objective related to gLOH scores, we first pursued a univariable linear regression. Next, we pursued a multivariable analysis for those biomarkers with > 5 events in the study population using a least absolute shrinkage and selection operator (LASSO) regression27 to exclude those gene alterations with a null impact in the model. Time to event end points was assessed using the Kaplan-Meier method and the log-rank test. Cox proportional-hazard models were used to obtain hazard ratios with 95% CIs. We relaxed the linearity assumption for gLOH using restricted cubic splines using the rms R package. The threshold for significance was set at 0.05 (two-sided) after adjustment. R v3.6.3 software program was used for all analyses.
9. This study was conducted according to the ethical principles for medical research described in the Declaration of Helsinki. Institutional review board approval of the study protocol and this analysis was obtained before study conduct and included a waiver of informed consent.
10. RESULTS
11. Sample and Patient Characteristics
12. We identified 1,847 cases with confirmed mPC who had been entered in the clinicogenomics integrated database between 2011 and 2021. After clinical data curation, 1,302 cases with follow-up clinical and treatment data available were retained for this analysis. Of those, genomic profiling had been pursued in tissue samples acquired either before any systemic therapy (ADT-naïve group, n = 840, 65%), after development of castration-resistance but before any NHT exposure (ADT-progression or CRPC group, n = 132, 10%), or after exposure to ≥ 1 NHT (NHT-CRPC group, n = 330, 25%; Fig 1). Five hundred seventeen (40%) cases were sequenced using the FoundationOne panel, and 785 (60%) using the later FoundationOne CDx panel. The median sequencing depth was 794× (interquartile range [IQR], 648-895), with no significant differences among samples in each of the three groups (median depth of 787×, 807×, and 805× for the ADT-naïve, ADT-progression, and NHT-exposed, respectively; see the Data Supplement for tumor content details).
13. The majority of samples in the ADT-naïve group were prostate primary tumor biopsies or radical prostatectomy specimens (674/840, 80%, v.20% of lymph nodes or other metastatic site biopsies), whereas in the post-NHT groups, biopsies were predominantly from lymph nodes (28%), liver (25%), or bone (16%) metastases, representing usual patterns of biopsy acquisition in real-world clinical practice. Patient and sample characteristics, as well as prior history...
of treatment exposure before the specimen acquisition are detailed in Table 1.

Figure 2 depicts the genomic landscape of the study cohort. Overall, 33% cases presented TMPRSS2 rearrangements. The prevalence of TP53 and RB1 aberrations was 41% and 5%, respectively. 33% cases showed PTEN loss-of-function alterations (truncating mutations or homozygous deletions) and 6% presented amplifications of activating mutations in PIK3CA. Among HRR-associated genes, 9% patients had deleterious BRCA2 aberrations, compared with 1.4% for BRCA1, 1% for PALB2, and 6% for ATM. Pathogenic mutations in CDK12 were detected in 7% of the overall population. Aberrations in MMR genes were infrequent (1.8% MSH2; 1.4% MSH6).

Associations Between Genomic Aberrations and Disease States
A significant enrichment in more advanced disease states (from ADT-naïve to CRPC and to NHT-CRPC) was observed for aberrations in AR (0.1% v 28% v 40%), MYC (5.5% v 18.2% v 20%), TP53 (35.4% v 47.7% v 51.5%), PTEN (27.6% v 38.6% v 36.4%), and RB1 (3.8% v 5.3% v 7.9%; all adjusted P values < .05; Fig 3A and 3B, Data Supplement). Combined inactivation of at least two among TP53, PTEN, and RB1 was also identified more frequently in later disease states: 12% ADT-naïve, 21% CRPC, and 22% NHT-CRPC (P < .001). Conversely, the prevalence of pathogenic events in BRCA2, ATM, and CDK12 were similar among disease states (all adjusted P values > .3), and overall prevalence of HRR pathway aberrations was 17% ADT-naïve versus 17% CRPC and 21% NHT-CRPC cases. We next looked at whether second BRCA2 allele loss could be detected in archival diagnostic samples. Biallelic loss was predicted in 58/72 (81%) of the ADT-naïve samples with BRCA2 deleterious mutations; in 5/72 (7%), there was no evidence of biallelic loss by NGS, whereas in 9/72 (12%), the bioinformatics algorithm could not confidently call zygosity. Similar trends were observed in the CRPC and NHT-CRPC groups, with 10/12 (83%) and 19/28 (68%) of BRCA2 mutated cases, respectively, showing evidence of biallelic loss by targeted NGS (Data Supplement). As observed in other series, the percentage of BRCA1-mutated cases predicted to harbor biallelic loss was lower (3/18; 17%).

The percentage of cases with tumor mutational burden ≥ 10 mutations/Mb was higher in the post-NHT-CRPC setting compared with the earlier settings (8.5% v 4.5% CRPC v 2.3% ADT-naïve; P < .001).

Genomic Landscape of ADT-Naïve, Primary Versus Metastatic Biopsies
Next, we focused on the ADT-naïve biopsy cohort (n = 840) to compare the genomic profile of primary prostate tumor (n = 674) versus metastatic (n = 166) biopsies. No significant differences were observed in primary versus metastasis in the prevalence of aberrations in TP53 (36.4% v 31.3%), PTEN (26.3% v 33.1%), BRCA2 (8.2% v 6.6%), or MYC (5% v 7.2%; all adjusted P values < .3; Fig 3C, Data Supplement). Considering pathway analyses, HRR-associated gene aberrations were also evenly distributed in primary versus metastatic ADT-naïve specimens (16% v 18%).

gLOH Score in Metastatic Prostate Cancer
A total of 847 specimens were evaluable for gLOH (65% of the overall study population; Data Supplement). The median gLOH score was 8.2% (IQR, 5.6%-11.5%). Later disease states were enriched for higher gLOH values: median 7.24% ADT-naïve, 8.92% CRPC (5.99-12.5), and 9.94% NHT-CRPC (7.14-13.6; P < .001). Higher gLOH score was associated with poor prognosis in the ADT-naïve group. Risks of CRPC progression or death were incrementally greater with increases in gLOH scores up to 10%, then reaching a plateau, whereas the association with the risk of death followed a near-linear increase (Data Supplement). If gLOH values were dichotomized on the basis of the median, higher gLOH values related to higher risk of progression to CRPC (hazard ratio = 1.26; 95% CI, 1.01 to 1.57; P = .03).

Next, we studied associations between gLOH scores and clinical and genomic features. In univariable analysis, aberrations in BRCA2 significantly associated with higher gLOH values (adjusted P < .001). Higher gLOH scores by means of more advanced disease states were observed for both BRCA2-aberrant and wild-type patient subgroups (Fig 4).

Beyond DDR genes, we also identified significant positive associations between gLOH score and aberrations in TP53.


(P < .001), RB1 (P < .001), AR (P < .001), and PTEN (P = .01) in univariate analysis. Conversely, significant inverse associations were identified between gLOH scores and mutations in CDK12, CTNNB1, and MSH2 (Data Supplement). We explored the features of those samples with higher gLOH scores; a threshold of gLOH = 13.6% defined the top quartile in our study population. Among those patients, and after excluding patients with canonical BRCA1/2 alterations, TP53 and MYC amplifications were significantly enriched (P-adjusted .001 for both).

To confirm these findings, we performed a multivariable analysis (MVA) including the clinical and genomic variables of interest (from the total gene list, we excluded those with ≤ 5 events and those showing high multicollinearity or null

---

**TABLE 1. Clinical Characteristics of the Study Population**

| Variable | ADT-Naïve (n = 840) | ADT-Progression (n = 132) | NHT-Exposed (n = 330) | Total (N = 1,302) | P |
|----------|---------------------|---------------------------|----------------------|-------------------|---|
| Specimen site |                      |                           |                      |                   | < .001 |
| Bladder  | 13 (1.5)            | 16 (12.1)                 | 18 (5.5)             | 47 (3.6)          |   |
| Bone     | 52 (6.2)            | 17 (12.9)                 | 53 (16.1)            | 122 (9.4)         |   |
| Liver    | 9 (1.1)             | 27 (20.5)                 | 83 (25.2)            | 119 (9.1)         |   |
| Lymph node | 57 (6.8)         | 25 (18.9)                 | 91 (27.6)            | 173 (13.3)        |   |
| Other    | 35 (4.2)            | 26 (19.7)                 | 67 (20.3)            | 128 (9.8)         |   |
| Prostate | 674 (80.2)          | 21 (15.9)                 | 18 (5.5)             | 713 (54.8)        |   |
| Specimen collection to NGS, months |                      |                           |                      |                   | < .001 |
| Median (Q1, Q3) | 18.8 (3.8, 40.2) | 2.1 (1.0, 10.2)          | 1.1 (0.8, 1.9)       | 6.9 (1.4, 27.1)   |   |
| Practice type |                   |                           |                      |                   | < .001 |
| Academic  | 260 (31.0)          | 16 (12.1)                 | 36 (10.9)            | 312 (24.0)        |   |
| Community | 580 (69.0)          | 116 (87.9)                | 294 (89.1)           | 990 (76.0)        |   |
| Race |                   |                           |                      |                   | .026 |
| AA       | 66 (7.9)            | 4 (3.0)                   | 32 (9.7)             | 102 (7.8)         |   |
| Asian    | 13 (1.5)            | 2 (1.5)                   | 5 (1.5)              | 20 (1.5)          |   |
| Other    | 108 (12.9)          | 22 (16.7)                 | 61 (18.5)            | 191 (14.7)        |   |
| Unknown  | 51 (6.1)            | 3 (2.3)                   | 12 (3.6)             | 66 (5.1)          |   |
| White    | 602 (71.7)          | 101 (76.5)                | 220 (66.7)           | 923 (70.9)        |   |
| PSA at specimen collection |                   |                           |                      |                   | < .001 |
| Median (Q1, Q3) | 74.8 (20.3, 308.9) | 14.6 (4.2, 85.8)         | 51.5 (10.4, 196.3)   | 60.0 (15.6, 246.2)|   |
| Missing  | 92                  | 9                        | 82                   | 183               |   |
| Histology |                   |                           |                      |                   | < .001 |
| Adenocarcinoma | 811 (96.5)    | 124 (93.9)                | 291 (88.2)           | 1,226 (94.2)      |   |
| Other, mixed histology or not specified | 29 (3.5)    | 8 (6.1)                   | 39 (11.8)            | 76 (5.8)          |   |
| Therapy exposure before specimen acquisition |                   |                           |                      |                   |   |
| Prior ADT exposure | 0          | 132 (100)                 | 330 (100)            |                   |   |
| Time to CRPC, months |               |                           |                      |                   |   |
| Median (Q1, Q3) | NA         | 41.6 (13.1, 101.1)        | 43.3 (15.8, 99.1)    |                   |   |
| Prior NHT exposure | 0          | 0                        | 330 (100)            |                   |   |
| Time on NHT, months |               |                           |                      |                   |   |
| Median (Q1, Q3) | NA         | NA                       | 13.6 (7.4, 26.5)     |                   |   |
| Prior taxane exposure | 0          | 40 (30.3)                 | 168 (50.9)           |                   |   |
| Prior platinum exposure | 0          | 6 (4.5)                   | 14 (4.2)             |                   |   |
| Prior Radium 223 exposure | 0          | 3 (2.3)                   | 44 (13.3)            |                   |   |

Abbreviations: AA, African American; ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; NA, not available; NGS, next-generation sequencing; NHT, novel hormonal therapy; PSA, prostate-specific antigen.
In the MVA, prior hormonal therapy and, particularly, having previously received and progressed to both ADT and NHT were independently associated with higher gLOH scores. By contrast, prior taxane exposure, or the primary versus metastatic origin of the tumor specimen, did not affect gLOH scores. Among the genes included in the MVA, aberrations in \textit{BRCA2}, \textit{FANCA}, \textit{PALB2}, \textit{TP53}, and \textit{RB1} also showed significant independent associations with increased gLOH scores. CDK12, \textit{CTNNB1}, and \textit{MSH2} mutations, and \textit{TMPRSS2-ERG} fusions, independently associated with lower gLOH scores (Fig 5). AR aberrations no longer associated with gLOH when considering prior treatment exposure in the MVA.

A sensitivity analysis was performed independently in the subsets of primary and metastatic samples, obtaining similar results in each subgroup (Data Supplement), further suggesting that it is treatment-driven pressure, rather than differences between anatomical locations, which drives the enrichment for higher gLOH scores.

**DISCUSSION**

Integrating genomics and clinical data is central to the development and clinical implementation of precision cancer medicine strategies.\textsuperscript{28} In this study, we leveraged a large ‘real-world’ cohort of clinically and genomically annotated mPC cases to assess how disease progression and androgen-targeted therapy–induced selective pressure may affect the evolving genomic landscape of lethal prostate cancer.

Importantly, all patients in our study including those who were ADT-naïve at the time of biopsy acquisition had confirmed progression to late-stage mPC. Prior comparisons of the genomic landscape studies of primary versus metastatic prostate tumors could be confounded by the inclusion of patients with localized prostate cancer who never developed recurrence.\textsuperscript{4} We identified no significant differences in the prevalence of key gene aberrations between primary and metastasis in ADT-naïve samples, suggesting that both might be similarly

![OncoPrint summarizing the genomic landscape of the study cohort.](image-url)
**FIG 3.** (A) Prevalence of clinically relevant genomic aberrations in the study population by clinical state at the time of sample acquisition (blue: ADT-naïve, n = 840; red: ADT-progression, n = 132; teal: post-NHT-CRPC, n = 330). Prevalence figures by site of biopsy (prostate vs. metastasis) in (B) all cases and in (C) ADT-naïve cases. *P < .05; **P < .001. ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; NHT, novel hormonal therapy.
informative in newly diagnosed mPC patients, a population for whom genomic testing is now recommended by clinical guidelines.\textsuperscript{12,29}

We found enrichment of aberrations in \textit{AR}, \textit{MYC}, tumor suppressor genes such as \textit{TP53} and \textit{RB1}, and of cell cycle and PI3K/PTEN pathway genes, from ADT-naïve to CRPC and NHT-CRPC disease, highlighting their relevance to lethal prostate cancer progression and drug-resistance.\textsuperscript{30-32} Conversely, the prevalence of aberrations in \textit{BRCA2} and other HRR genes remained stable along disease progression. Even if some of these HRR gene mutations were of germline origin, we also observed that loss of the second allele in the tumor was detected similarly in pretreatment and postresistance biopsies.

Our study lacks longitudinal same-patient biopsies collected over time, as repeated genomic profiling is not commonly obtained in routine clinical practice; we compared samples from different patients. We and others have recently reported small series of patient-matched tumor tissue biopsies\textsuperscript{15,33} or correlative tumor-plasma paired samples\textsuperscript{34} that also suggest that HRR mutations are present in early stages of mPC progression. Our study complements this evidence with a much larger cohort, albeit with indirect comparisons. Together, these data support the use of diagnostic, archival tissue biopsies to stratify patients with metastatic castration-resistant prostate cancer for PARP inhibitor treatment on the basis of HRR gene status, regardless of later exposures to subsequent lines of therapy.\textsuperscript{6,7,35} Contrarily, assessment of \textit{AR} and cell-cycle–related genomic biomarkers may require contemporaneous specimens.

Patterns of genome-wide aberrations such as gLOH may help toward further clinical qualification of less common

\textbf{FIG 4.} gLOH distribution by clinical state: (A) histogram of gLOH scores in the overall study population, by disease states at the time of sample acquisition, and (B) boxplots comparing gLOH scores. ADT, androgen deprivation therapy; gLOH, genome-wide loss-of-heterozygosity; NHT, novel hormonal therapy.
HRR gene aberrations beyond BRCA2 mutations. We found that progression to hormonal therapy, but not to taxanes, associates with increasing gLOH scores independent of specific HRR gene aberrations or subtypes; and that TP53 or RB1 loss, which is also more prevalent in later disease stages, independently contributes to increased gLOH scores. This increase with mPC hormonal resistance possibly reflects positive selection of genomically unstable subclones, in line with the increased level of large-scale transition (LST) events, another candidate marker of genomic instability, shown in liquid biopsies in later stages of mPC.36,37 On the basis of these findings, clinical trials evaluating PARP inhibitor as monotherapy or in combination in prostate cancer should take into consideration the time of biopsy acquisition and the TP53 and RB1 mutational status when analyzing the predictive value of gLOH scores.

We acknowledge that the retrospective nature of our study prevented us from controlling for potential confounding factors, although access to correlative clinical annotations allowed us to adjust gene-specific analyses to distinct clinical states. Moreover, different from previous studies, our cohort was formed by patients receiving treatment mostly in community practices and not in academic centers, including a wide range of institutions not involved in clinical trials. As genomic testing becomes part of the standard prostate cancer patient journey, real-world data sets including patients under-represented in research studies (ie, those with comorbidities, poor performance status, elderly, or minorities38 on the basis of geographical,

| Variable                      | No. | Estimate | Estimate (95% CI) | P      |
|-------------------------------|-----|----------|------------------|--------|
| Prior hormonal therapy        |     |          |                  |        |
| ADT-naive                     | 480 |          |                  |        |
| ADT-progression               | 104 |          | 1.05 (−0.05 to 2.15) | .060 |
| NHT-exposed                   | 263 |          | 2.08 (1.06 to 3.10) | < .001|
| Biopsy site                   |     |          |                  |        |
| Metastatic                    | 477 |          |                  |        |
| Prostate                      | 370 |          | −0.65 (−1.44 to 0.14) | .105 |
| Prior taxane                  |     |          |                  |        |
| No                            | 679 |          |                  |        |
| Yes                           | 168 |          | 0.70 (−0.21 to 1.60) | .130 |
| AKT1 short variant            | 17  |          | 0.71 (−1.36 to 2.77) | .502 |
| APC alteration                 | 69  |          | 0.46 (−0.62 to 1.53) | .403 |
| AR amplification              | 141 |          | −0.42 (−1.34 to 0.50) | .374 |
| ATM alteration                 | 50  |          | 1.43 (0.16 to 2.69) | .027 |
| BRAF short variant            | 15  |          | −0.19 (−2.39 to 2.00) | .862 |
| BRCA1 alteration              | 9   |          | 1.82 (−1.05 to 4.70) | .214 |
| BRCA2 alteration              | 65  |          | 1.74 (0.64 to 2.85) | .002 |
| CDK12 alteration              | 58  |          | −3.03 (−4.22 to −1.83) | < .001|
| CDK4/6 amplification          | 31  |          | −0.80 (−2.35 to 0.75) | .313 |
| CHEK2 alteration              | 16  |          | −0.41 (−2.53 to 1.71) | .705 |
| CTNNB1 short variant          | 32  |          | −2.19 (−3.72 to −0.65) | .006 |
| FANCA alteration              | 7   |          | 3.79 (0.60 to 6.99) | .020 |
| MSH2 alteration               | 13  |          | −3.85 (−6.27 to −1.43) | .002 |
| PALB2 alteration              | 8   |          | 3.19 (0.18 to 6.20) | .038 |
| PTEN alteration               | 294 |          | 0.18 (−0.45 to 0.81) | .574 |
| RB1 alteration                | 60  |          | 2.18 (1.04 to 3.33) | < .001|
| TMPRSS2–ERG fusion            | 246 |          | −1.12 (−1.78 to −0.46) | < .001|
| TP53 alteration               | 351 |          | 1.43 (0.80 to 2.06) | < .001|

FIG 5. Clinical features and genomic alterations associated with gLOH. A multivariable model was constructed to evaluate the associations of clinical and genomic variables with gLOH. Point estimates and confidence intervals indicate the average difference in gLOH independently associated with each feature. For genomic aberrations, the reference is wild-type. The threshold for significance was established at adjusted P < .05 (two-sided). The dashed line represents a null association; squares (and CI) to the right represent a direct association of the variable with higher gLOH, whereas squares (and CI) to the left indicate an inverse association between the variable and gLOH levels. ADT, androgen deprivation therapy; gLOH, genome-wide loss-of-heterozygosity; NHT, novel hormonal therapy.
ethnicity, or socioeconomic factors) will become critical to inform strategies for delivering precision medicine in diverse clinical settings.

In conclusion, prevalence of mutations in BRCA2 and other HRR-associated genes is stable along mPC progression, supporting the use of diagnostic tumor biopsies for mPC patient stratification for PARP inhibitor treatment in clinical practice after progression to NHT. Progression to androgen-targeted therapies is linked to enrichment in AR, MYC, TP53, PTEN, RB1, and PI3K/PTEN pathway aberrations, as well as in genomic instability as per increasing gLOH scores, independent of BRCA1/2 status.

AFFILIATIONS
1The University of Texas MD Anderson Cancer Center, Houston, TX
2Foundation Medicine Inc, Cambridge, MA
3Vall d’Hebron Institute of Oncology (VHIO) and Vall d’Hebron University Hospital Campus, Barcelona, Spain
4University of Minnesota, Masonic Cancer Center, Minneapolis, MN
5SUNY Upstate Medical University, Syracuse, NY

CORRESPONDING AUTHOR
Joaquin Mateo, MD, PhD, Department of Medical Oncology, Vall d’Hebron University Hospital Prostate Cancer Translational Research Group, Vall d’Hebron Institute of Oncology (VHIO), 115-117 Natzaret, Cellex Center, 402; 08035 Barcelona, Spain; Twitter: @quimmmateo; e-mail: jmateo@vhio.net.

EQUAL CONTRIBUTION
A.J.Z. and R.P.G. contributed equally to this work and are joint first authors. A.J.Z. and J.M. supervised this work and are joint senior authors.

PRIOR PRESENTATION
Presented at the ASCO GU Cancers Symposium, San Francisco, CA, February 17, 2022.

SUPPORT
Supported by Foundation Medicine, Inc.

AUTHOR CONTRIBUTIONS
Conception and design: Amado J. Zurita, Ryon P. Graf, Emmanuel S. Antonarakis, Jeffrey S. Ross, Joaquin Mateo
 Provision of study materials or patients: Ryon P. Graf, Joaquin Mateo
 Collection and assembly of data: Amado J. Zurita, Ryon P. Graf, Guillermo Villacampa, Kira Raskina, Emmanuel S. Antonarakis, Jeffrey S. Ross, Joaquin Mateo
 Data analysis and interpretation: All authors
 Manuscript writing: All authors
 Final approval of manuscript: All authors
 Accountable for all aspects of the work: All authors

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. 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/po/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Amado J. Zurita
 Honoraria: Pfizer, Janssen
 Consulting or Advisory Role: AstraZeneca, Bayer

Research Funding: Infinity Pharmaceuticals
Ryon P. Graf
Employment: Foundation Medicine, Epic Sciences
Stock and Other Ownership Interests: Roche
Travel, Accommodations, Expenses: Epic Sciences, Foundation Medicine
Guillermo Villacampa
Consulting or Advisory Role: AstraZeneca, GlaxoSmithKline
Speakers’ Bureau: MSD Oncology, Pierre Fabre
Kira Raskina
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Patents, Royalties, Other Intellectual Property: Submitted patent for HRD calling methodology (Inst)
Dexter Jin
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology, Amgen, Bayer, Blue Earth Diagnostics, Bristol Myers Squibb/Celgene, Celgene, Constellation Pharmaceuticals, Curium Pharma, Lilly, Exact Sciences, Foundation Medicine, GlaxoSmithKline, InVitae, ISMAR Health Care, Tempus
Consulting or Advisory Role: Sanofi, Dendreon, Janssen Biotech, ESSA, Merck, AstraZeneca, Clovis Oncology, Lilly, Bayer, Amgen, Astellas Pharma, Blue Earth Diagnostics, Bristol Myers Squibb/Celgene, Constellation Pharmaceuticals, Curium Pharma, Exact Sciences, Foundation Medicine, GlaxoSmithKline, InVitae, ISMAR Health Care, Medivation, Tempus
Research Funding: Janssen Biotech (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst), Merck (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst), Celgene, Clovis Oncology
Patents, Royalties, Other Intellectual Property: Coinventor of a biomarker technology that has been licensed to Qiagen
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation
Gerald Li
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Richard S. P. Huang
Employment: Roche/Foundation Medicine
Stock and Other Ownership Interests: Roche
Patents, Royalties, Other Intellectual Property: Patent on IHC, provisional patent on biomarkers and biomarker methodology

Research Funding: Infinity Pharmaceuticals
Ryon P. Graf
Employment: Foundation Medicine, Epic Sciences
Stock and Other Ownership Interests: Roche
Travel, Accommodations, Expenses: Epic Sciences, Foundation Medicine
Guillermo Villacampa
Consulting or Advisory Role: AstraZeneca, GlaxoSmithKline
Speakers’ Bureau: MSD Oncology, Pierre Fabre
Kira Raskina
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Patents, Royalties, Other Intellectual Property: Submitted patent for HRD calling methodology (Inst)
Dexter Jin
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology, Amgen, Bayer, Blue Earth Diagnostics, Bristol Myers Squibb/Celgene, Celgene, Constellation Pharmaceuticals, Curium Pharma, Lilly, Exact Sciences, Foundation Medicine, GlaxoSmithKline, InVitae, ISMAR Health Care, Tempus
Consulting or Advisory Role: Sanofi, Dendreon, Janssen Biotech, ESSA, Merck, AstraZeneca, Clovis Oncology, Lilly, Bayer, Amgen, Astellas Pharma, Blue Earth Diagnostics, Bristol Myers Squibb/Celgene, Constellation Pharmaceuticals, Curium Pharma, Exact Sciences, Foundation Medicine, GlaxoSmithKline, InVitae, ISMAR Health Care, Medivation, Tempus
Research Funding: Janssen Biotech (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst), Merck (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst), Celgene, Clovis Oncology
Patents, Royalties, Other Intellectual Property: Coinventor of a biomarker technology that has been licensed to Qiagen
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation
Gerald Li
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Richard S. P. Huang
Employment: Roche/Foundation Medicine
Stock and Other Ownership Interests: Roche
Patents, Royalties, Other Intellectual Property: Patent on IHC, provisional patent on biomarkers and biomarker methodology

Research Funding: Infinity Pharmaceuticals
Ryon P. Graf
Employment: Foundation Medicine, Epic Sciences
Stock and Other Ownership Interests: Roche
Travel, Accommodations, Expenses: Epic Sciences, Foundation Medicine
Guillermo Villacampa
Consulting or Advisory Role: AstraZeneca, GlaxoSmithKline
Speakers’ Bureau: MSD Oncology, Pierre Fabre
Kira Raskina
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Patents, Royalties, Other Intellectual Property: Submitted patent for HRD calling methodology (Inst)
Dexter Jin
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Emmanuel S. Antonarakis
Honoraria: Sanofi, Dendreon, Medivation, Janssen Biotech, ESSA, Astellas Pharma, Merck, AstraZeneca, Clovis Oncology, Amgen, Bayer, Blue Earth Diagnostics, Bristol Myers Squibb/Celgene, Celgene, Constellation Pharmaceuticals, Curium Pharma, Lilly, Exact Sciences, Foundation Medicine, GlaxoSmithKline, InVitae, ISMAR Health Care, Tempus
Consulting or Advisory Role: Sanofi, Dendreon, Janssen Biotech, ESSA, Merck, AstraZeneca, Clovis Oncology, Lilly, Bayer, Amgen, Astellas Pharma, Blue Earth Diagnostics, Bristol Myers Squibb/Celgene, Constellation Pharmaceuticals, Curium Pharma, Exact Sciences, Foundation Medicine, GlaxoSmithKline, InVitae, ISMAR Health Care, Medivation, Tempus
Research Funding: Janssen Biotech (Inst), Johnson & Johnson (Inst), Sanofi (Inst), Dendreon (Inst), Aragon Pharmaceuticals (Inst), Exelixis (Inst), Millennium (Inst), Genentech (Inst), Novartis (Inst), Astellas Pharma (Inst), Tokai Pharmaceuticals (Inst), Merck (Inst), AstraZeneca (Inst), Clovis Oncology (Inst), Constellation Pharmaceuticals (Inst), Celgene, Clovis Oncology
Patents, Royalties, Other Intellectual Property: Coinventor of a biomarker technology that has been licensed to Qiagen
Travel, Accommodations, Expenses: Sanofi, Dendreon, Medivation
Gerald Li
Employment: Foundation Medicine
Stock and Other Ownership Interests: Roche
Richard S. P. Huang
Employment: Roche/Foundation Medicine
Stock and Other Ownership Interests: Roche
Patents, Royalties, Other Intellectual Property: Patent on IHC, provisional patent on biomarkers and biomarker methodology
REFERENCES

1. Robinson D, Van Allen EM, Wu YM, et al: Integrative clinical genomics of advanced prostate cancer. Cell 161:1215-1228, 2015
2. Quigley DA, Dang HX, Zhao SG, et al: Genomic hallmarks and structural variation in metastatic prostate cancer. Cell 174:758-769, 2018
3. Stopa-Sack KH, Nandakumar S, Wibmer AG, et al: Oncogenic genomic alterations, clinical phenotypes, and outcomes in metastatic castration-sensitive prostate cancer. Clin Cancer Res 26:3230-3238, 2020
4. Armenia J, Wankowicz SAM, Liu D, et al: Long tail of oncogenic drivers in prostate cancer. Nat Genet 50:645-651, 2018
5. de Bono J, Mateo J, Fizazi K, et al: Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med 382:2091-2102, 2020
6. de Bono J, Fizazi K, et al: For metastatic castration-resistant prostate cancer. N Engl J Med 382:2091-2102, 2020
7. Abida W, Cheng ML, Armenia J, et al: Analysis of the prevalence of microsatellite instability in prostate cancer and response to immune checkpoint blockade. JAMA Oncol 3:3753-3758, 2019
8. Marcus L, Lemery SJ, Keegan P, et al: FDA approval summary: Pembrolizumab for the treatment of microsatellite instability-high solid tumors. Clin Cancer Res 25:3753-3758, 2019
9. de Bono JS, Sweeney C, Bicciard E, et al: PIK3CA/KT pathway biomarkers analysis from the phase III IPATential150 trial of ipatasertib plus abiraterone in metastatic castration-resistant prostate cancer. J Clin Oncol 39, 2021 (suppl 6, abstr 13)
10. Antonaraks ES, Lu C, Wang H, et al: AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med 371:1028-1038, 2014
11. Parker C, Castro E, Fizazi K, et al: Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 31:1119-1134, 2020
12. Conford P, van der Bergh RCN, Briers E, et al: EAU-EANM-ESTRO-SIOG guidelines on prostate cancer. Part II-2020 update: Treatment of relapsing and metastatic prostate cancer. Eur Urol 79:263-282, 2021
13. Schaeffer E, Srinivas S, Antonaraks ES, et al: NCCN guidelines insights: Prostate cancer, version 1.2021. J Natl Compr Canc Netw 19:134-143, 2021
14. Mateo J, Seid G, Berton C, et al: Genomics of lethal prostate cancer at diagnosis and castration resistance. J Clin Invest 130:1743-1751, 2020
15. Annala M, Vandekerkhove G, Khalaf D, et al: Circulating tumor DNA genomics correlate with resistance to abiraterone and enzalutamide in prostate cancer. Cancer Discov 8:444-457, 2018
16. Romanel A, Ossensi T, Conteduca V, et al: Plasmar AR and abiraterone-resistant prostate cancer. Sci Transl Med 7:312re10, 2015
17. Mateo J, Porta N, Bianchini D, et al: Olaparib in patients with metastatic castration-resistant prostate cancer with DNA repair gene aberrations (TOPARP-B): A multicentre, open-label, randomised, phase 2 trial. Lancet Oncol 21:162-174, 2020

ACKNOWLEDGMENT

The authors thank the patients whose data made this research possible, the clinical, laboratory, and data staff at Foundation Medicine, and the team at Flatiron Health. The authors affiliated to VHIO acknowledge support from La Caixa Foundation (CaixaResearch Advanced Oncology Research Program), FERO, and Fundación Cellex. I. Casanova-Salas is supported by the La Caixa Foundation and the European Union’s Horizon 2020 research and innovation program (LCF/BQ/P120/11760033). J. Mateo acknowledges support from the CRS Cancer Foundation (PR_TCL_2020_10), Instituto de Salud Carlos III, Fundación AECC (LABAEE20019MATE), and the US Department of Defense CDMRP (PC170510P1 Impact Award). A. Zurita-Saavedra acknowledges support from the MD Anderson Prostate Cancer Moonshot Program.

Ana Vivancos

Stock and Other Ownership Interests: Reveal Genomics

Consulting or Advisory Role: Guardant Health, Merck, Roche, Bristol Myers Squibb, Incyte, Bayer

Research Funding: Bristol Myers Squibb (Inst), Roche (Inst), Incyte (Inst)

Joan Carles

Consulting or Advisory Role: Bayer, Johnson & Johnson/Janssen, Bristol Myers Squibb, Astellas Pharma, Sanofi, MSD Oncology, Roche, AstraZeneca, Advanced Accelerator Applications/Novartis, Pfizer

Speakers' Bureau: Bayer, Johnson & Johnson, Astellas Pharma

Research Funding: AB Science Inc, Aragon Pharmaceuticals (Inst), Arog (Inst), Astellas Pharma (Inst), AstraZeneca (Inst), AVEO (Inst), Bayer (Inst), Blueprint Medicines (Inst), BN Immunotherapeutics (Inst), Boehringer Ingelheim (Inst), Bristol Myers Squibb International Corporation (BMS) (Inst), Clovis Oncology (Inst), Cougar Biotechnology (Inst), Deciphera, Exelixis (Inst), Roche (Inst), Genentech (Inst), GlaxoSmithKline (Inst), Incyte (Inst), Janssen-Cilag International NV (Inst), Karsopharm Therapeutics (Inst), Laboratories Leurquin Mediolanum (Inst), Lilly (Inst), Medimmune (Inst), Millenium Pharmaceuticals (Inst), Nanobiotix (Inst), Novartis FarmaAcutica SA (Inst), Pfizer (Inst), Puma Biotechnology (Inst), Sanofi Aventis GmbH (Inst), SFI Pharmaceuticals Group (Inst), Teva (Inst)

Travel, Accommodations, Expenses: BMS, Ipsen, Roche, AstraZeneca

Jeffrey S. Ross

Employment: Foundation Medicine

Leadership: Foundation Medicine

Stock and Other Ownership Interests: Foundation Medicine

Consulting or Advisory Role: Celsius Therapeutics, Tango Therapeutics

Research Funding: Foundation Medicine

Alexa B. Schrock

Employment: Foundation Medicine

Stock and Other Ownership Interests: Foundation Medicine, Roche

Geoffrey R. Oxnard

This author is a member of the JCO Precision Oncology Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.

Employment: Foundation Medicine

Stock and Other Ownership Interests: Roche

Joaquin Mateo

This author is a member of the JCO Precision Oncology Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.

Consulting or Advisory Role: AstraZeneca, Roche, MSD, Amgen, Pfizer, Daiichi Sankyo

Speakers’ Bureau: AstraZeneca, Astellas, Janssen, Pfizer, Guardant Health

Research Funding: AstraZeneca (Inst), Pfizer (Inst)

Travel, Accommodations, Expenses: AstraZeneca

No other potential conflicts of interest were reported.

No potential conflicts of interest were reported.

No other potential conflicts of interest were reported.

No other potential conflicts of interest were reported.

No other potential conflicts of interest were reported.
19. Abkevich V, Timms KM, Hennessy BT, et al: Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer. Br J Cancer 107:1776-1782, 2012
20. Sokol ES, Pavlick D, Khiabanian H, et al: Pan-cancer analysis of BRCA1 and BRCA2 genomic alterations and their association with genomic instability as measured by genome-wide loss of heterozygosity. JCO Precis Oncol 4:442-465, 2020
21. Swisher EM, Lin KK, Oza AM, et al: Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): An international, multicentre, open-label, phase 2 trial. Lancet Oncol 18:75-87, 2017
22. Jonsson P, Bandlamudi C, Cheng ML, et al: Tumour lineage shapes BRCA-mediated phenotypes. Nature 571:576-579, 2019
23. Westphalen CB, Fine AD, Andre F, et al: Pan-cancer analysis of homologous recombination repair-associated gene alterations and genome-wide loss of heterozygosity score. Clin Cancer Res 28:1412-1421, 2022
24. Frampton GM, Fichtenholtz A, Otto GA, et al: Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 31:1023-1031, 2013
25. Chalmers ZR, Connelly CF, Fabrizio D, et al: Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. Genome Med 9:34, 2017
26. Coleman RL, Oza AM, Lorusso D, et al: Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): A randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 390:1949-1961, 2017
27. Tibshirani R: Regression shrinkage and selection via the Lasso. J R Statist Soc B 58:267-288, 1996
28. Mateo J, McKay R, Abida W, et al: Accelerating precision medicine in metastatic prostate cancer. Nat Cancer 1:1041-1053, 2020
29. Moslehi F, Remon J, Mateo J, et al: Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: A report from the ESMO Precision Medicine Working Group. Ann Oncol 31:1491-1505, 2020
30. Hamid AA, Gray KP, Shaw G, et al: Compound genomic alterations of TP53, PTEN, and RB1 tumor suppressors in localized and metastatic prostate cancer. Eur Urol 76:89-97, 2019
31. Chen WS, Aggarwal R, Zhang L, et al: Genomic drivers of poor prognosis and enzalutamide resistance in metastatic castration-resistant prostate cancer. Eur Urol 76:562-571, 2019
32. Mu P, Zhang Z, Benelli M, et al: SOX2 promotes lineage plasticity and antiandrogen resistance in TP53- and RB1-deficient prostate cancer. Science 355:84-88, 2017
33. Schweizer MT, Sivakumar S, Tukachinsky H, et al: Concordance of DNA repair gene mutations in paired primary prostate cancer samples and metastatic tissue or cell-free DNA. JAMA Oncol 7:1378-1382, 2021
34. Warner E, Herberts C, Fu S, et al: BRCA2, ATM, and CDK12 defects differentially shape prostate tumor driver genomics and clinical aggression. Clin Cancer Res 27:1650-1662, 2021
35. Hussain M, Mateo J, Fizazi K, et al: Survival with olaparib in metastatic castration-resistant prostate cancer. N Engl J Med 383:2345-2357, 2020
36. Sumana-suriya S, Seed G, Parr H, et al: Elucidating prostate cancer behaviour during treatment via low-pass whole-genome sequencing of circulating tumour DNA. Eur Urol 80:243-253, 2021
37. Malihi PD, Graf RP, Rodriguez A, et al: Single-cell circulating tumor cell analysis reveals genomic instability as a distinctive feature of aggressive prostate cancer. Clin Cancer Res 26:4143-4153, 2020
38. Mahal BA, Alshalalfa M, Kessler KH, et al: Racial differences in genomic profiling of prostate cancer. N Engl J Med 383:1083-1085, 2020