# Impact of FANCA, ATM, CDK12 Alterations on Survival in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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## Introduction

- Alterations (alt) in non-BRCA HRR genes represent a heterogeneous group that may impact the outcome of mCRPC patients. The clinical significance of each individual gene is poorly understood.
- We have recently reported on the adverse prognostic value of BRCA gene alterations in mCRPC patients, compared with both patients without HRR alterations and with non-BRCA HRR alterations[1].
- In the current study, we investigated the impact of individual non-BRCA HRR alterations on the outcome of patients with mCRPC treated with 1L novel hormonal therapy (NHT) or taxanes.

## Methods

- Eligible pts from PROREPAIR-B (NCT03075735), PROSENZA (NCT02922218), PROSTAC (NCT02362620), and PROSABI (NCT02787837) studies underwent paired somatic/germline DNA analyses using a custom NGS panel that included ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2, RAD51B, and RAD54L.

## Methods

- Pts were classified as non-BRCA HRR (ATM, FANCA, CDK12, other genes) if a pathogenic or likely pathogenic alt in ≥1 allele and **no concomitant BRCA alt** were present.
- rPFS and OS were reported for BRCA, each of the non-BRCA HRR alterations and non-HRR subgroups; association with outcome was assessed using multivariable (MV) Cox-regression models including baseline variables with known prognostic value.
  - Prognostic variables in the MV model included age, stage IV at diagnosis, baseline albumin, hemoglobin, ALP, LDH and PSA, ECOG status, Gleason Score, number of bone metastases, visceral metastases time from start of ADT to mCRPC and choice of first-line therapy (Table 1).
  - Hazard ratios (HR) with 95% confidence intervals (95%CI) and p-values (p) are summarized in Table 2

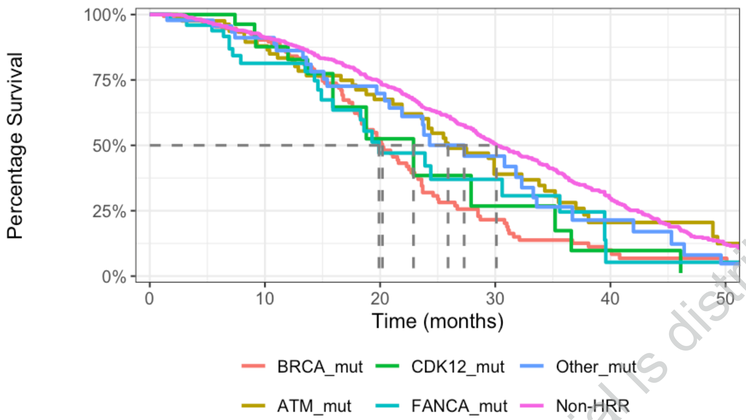
## Results

- Of the 729 pts, 223 (30.6%) were HRR, including 96 (13.2%) BRCA, 52 (7.3%) ATM, 26 (3.2%) FANCA, 14 (2%) CDK12 and 34 (4.8%) pts with other HRR non-BRCA alterations. 1 pt with co-occuring FANCA + CDK12 mutation was excluded.

After adjusting for baseline covariates (Table 2):

- Pts with ATM mutations experienced improved outcomes compared with BRCA (HR 0.65; p=0.035) and no significant difference compared with non-HRR (HR 1.25; p=0.17).
- FANCA (HR 0.97; p=0.91) and CDK12 (HR 1.38; p=0.37) mutants showed no difference in OS when compared to pts with BRCA mutations.
- Similar results were observed when evaluating rPFS (Table 2)
- 95%CI of HRs are relatively wide due to the low number of patients in each subgroup

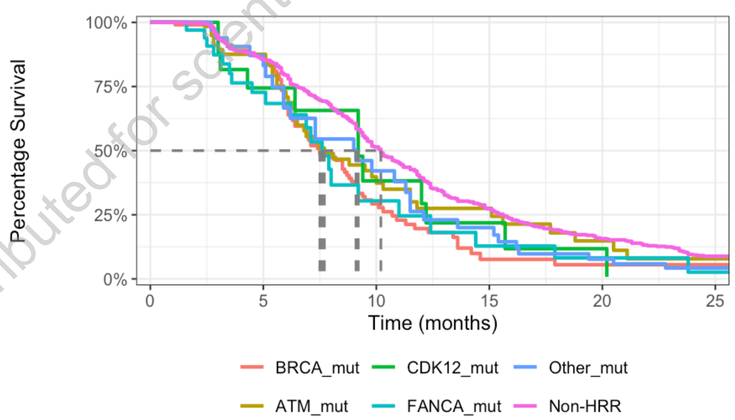
**FIGURE 1. OVERALL SURVIVAL**




| At Risk | | | | | | |
|---|---|---|---|---|---|---|
| BRCA_mut | 96 | 82 | 41 | 15 | 6 | 4 |
| ATM_mut | 52 | 43 | 31 | 14 | 6 | 3 |
| CDK12_mut | 14 | 11 | 6 | 3 | 1 | 0 |
| FANCA_mut | 26 | 18 | 8 | 5 | 1 | 1 |
| Other_mut | 34 | 30 | 22 | 15 | 6 | 2 |
| Non-HRR | 506 | 450 | 354 | 234 | 128 | 48 |

*Kaplan Meier curves represent observed data and are not adjusted*

**FIGURE 2. RADIOGRAPHIC PROGRESSION-FREE SURVIVAL**




| At Risk | | | | | | |
|---|---|---|---|---|---|---|
| BRCA_mut | 94 | 78 | 20 | 6 | 5 | 3 |
| ATM_mut | 52 | 42 | 16 | 10 | 4 | 1 |
| CDK12_mut | 14 | 10 | 5 | 3 | 1 | 0 |
| FANCA_mut | 25 | 15 | 7 | 4 | 2 | 1 |
| Other_mut | 33 | 28 | 17 | 11 | 6 | 3 |
| Non-HRR | 505 | 414 | 242 | 149 | 104 | 65 |

**TABLE 1. PATIENT CHARACTERISTICS**

| | | Non-HRR (N=506) | BRCA (N=96) | ATM (N=52) | CDK12 (N=14) | FANCA (N=26) | Other (N=34) |
|---|---|---|---|---|---|---|---|
| Age (yr) | <65 | 114 (23%) | 16 (17%) | 18 (35%) | 5 (36%) | 7 (27%) | 5 (15%) |
| | 65-75 | 201 (40%) | 41 (43%) | 20 (39%) | 2 (14%) | 11 (42%) | 14 (41%) |
| | >=75 | 191 (38%) | 39 (41%) | 14 (27%) | 7 (50%) | 8 (31%) | 15 (44%) |
| Stage IV at diagnosis | | 244 (48%) | 41 (43%) | 22 (42%) | 5 (36%) | 18 (69%) | 13 (38%) |
| Albumin < 4 g/dL | | 181 (36%) | 46 (48%) | 13 (25%) | 5 (36%) | 12 (46%) | 14 (41%) |
| ALP ≥ ULN | | 237 (47%) | 58 (60%) | 35 (67%) | 6 (43%) | 15 (58%) | 13 (38%) |
| Hb ≤ 12.5 | | 185 (37%) | 40 (42%) | 16 (31%) | 6 (43%) | 10 (39%) | 11 (32%) |
| LDH ≥ ULN | | 225 (45%) | 46 (48%) | 31 (60%) | 7 (50%) | 14 (54%) | 17 (50%) |
| PSA > 50 ng/dL | | 180 (36%) | 41 (43%) | 23 (44%) | 8 (57%) | 13 (50%) | 11 (32%) |
| ECOG | >=1 | 268 (53%) | 52 (54%) | 28 (54%) | 8 (57%) | 14 (54%) | 16 (47%) |
| | 0 | 238 (47%) | 44 (46%) | 24 (46%) | 6 (43%) | 12 (46%) | 18 (53%) |
| Gleason Score >= 8 | | 318 (63%) | 63 (66%) | 33 (64%) | 11 (79%) | 22 (85%) | 15 (44%) |
| Bone metastases > 10 | | 86 (17%) | 18 (19%) | 8 (15%) | 3 (21%) | 9 (35%) | 4 (12%) |
| Visceral metastases | | 70 (14%) | 9 (9%) | 3 (6%) | 5 (36%) | 4 (15%) | 6 (18%) |
| Time to mCRPC ≥ median | | 268 (53%) | 42 (44%) | 20 (39%) | 8 (57%) | 8 (31%) | 20 (59%) |
| 1st line therapy | Taxanes | 200 (40%) | 34 (35%) | 25 (48%) | 5 (36%) | 13 (50%) | 12 (35%) |
| | ARSIs | 306 (60%) | 62 (65%) | 28 (52%) | 9 (64%) | 13 (50%) | 22 (65%) |

**TABLE 2. IMPACT OF NON-BRCA MUTATION STATUS ON OS AND RPFS (MULTIVARIABLE MODEL)**

| | Median (95%CI) | HR (95%CI) vs BRCA | HR (95%CI) vs non-HRR |
|---|---|---|---|
| **OVERALL SURVIVAL** | | | |
| **Non-HRR** | 29.6 m (27.9-32.1) | - | - |
| **BRCA** | 18.4 m (16.7-20.2) | - | - |
| **ATM** | 24.2 m (17.9-29.4) | 0.65 (0.43-0.97); p=0.035 | 1.25 (0.9-1.7); p=0.17 |
| **CDK12** | 17.4 m (9.2-35.2) | 1.38 (0.68-2.8); p=0.37 | 2.1 (1.2-3.6); p=0.015 |
| **FANCA** | 17.1 m (7.9-23.9) | 0.97 (0.58-1.62); p=0.91 | 1.9 (1.2-2.9); p=0.003 |
| **Other** | 24 m (15-33) | 0.66 (0.4-1); p=0.07 | 1.3 (0.9-1.9); p=0.139 |
| **RADIOGRAPHIC PROGRESSION-FREE SURVIVAL** | | | |
| **Non-HRR** | 11 m (10.1-12) | - | - |
| **BRCA** | 7.1 m (6.2-8.5) | - | - |
| **ATM** | 7.7 m (6.4-10.3) | 0.76 (0.5-1.2); p=0.194 | 1.37 (0.98-1.9); p=0.07 |
| **CDK12** | 9.2 (3.1-12.2) | 1.33 (0.6-2.9); p=0.48 | 1.54 (0.8-2.9); p=0.167 |
| **FANCA** | 7.1 (3.6-11) | 1.1 (0.64-1.8); p=0.77 | 1.9 (1.2-3); p=0.004 |
| **Other** | 11 (7.3-15.2) | 0.81 (0.5-1.3); p=0.386 | 1.4 (0.97-2.1); p=0.07 |

## Conclusions

- FANCA, ATM and CDK12 alterations are associated with different outcomes.
- The marked heterogeneity in may not justify pooling non-BRCA HRR alterations into a unified entity.
- Results are limited by the small sample size, especially in the CDK12 mut subgroup
- Further studies are needed to elucidate the clinical significance of each alteration independently.

**References** (1) Olmos et al. Ann Oncol 2024

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