Memorial Sloan Kettering Cancer Center

# DNA Repair in Prostate Cancer

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Chairman Department of Medicine
Memorial Sloan Kettering Cancer Center

Volume 161, Issue 5, p1215–1228, 21 May 2015



Resource

# Integrative Clinical Genomics of Advanced Prostate Cancer

Dan Robinson[43], Eliezer M. Van Allen[43], Yi-Mi Wu, Nikolaus Schultz, Robert J. Lonigro, Juan-Miguel Mosquera, Bruce Montgomery, Mary-Ellen Taplin, Colin C. Pritchard, Gerhardt Attard, Himisha Beltran, Wassim Abida, Robert K. Bradley, Jake Vinson, Xuhong Cao, Pankaj Vats, Lakshmi P. Kunju, Maha Hussain, Felix Y. Feng, Scott A. Tomlins, Kathleen A. Cooney, David C. Smith, Christine Brennan, Javed Siddiqui, Rohit Mehra, Yu Chen, Dana E. Rathkopf, Michael J. Morris, Stephen B. Solomon, Jeremy C. Durack, Victor E. Reuter, Anuradha Gopalan, Jianjiong Gao, Massimo Loda, Rosina T. Lis, Michaela Bowden, Stephen P. Balk, Glenn Gaviola, Carrie Sougnez, Manaswi Gupta, Evan Y. Yu, Elahe A. Mostaghel, Heather H. Cheng, Hyojeong Mulcahy, Lawrence D. True, Stephen R. Plymate, Heidi Dvinge, Roberta Ferraldeschi, Penny Flohr, Susana Miranda, Zafeiris Zafeiriou, Nina Tunariu, Joaquin Mateo, Raquel Perez-Lopez, Francesca Demichelis, Brian D. Robinson, Marc Schiffman, David M. Nanus, Scott T. Tagawa, Alexandros Sigaras, Kenneth W. Eng, Olivier Elemento, Andrea Sboner, Elisabeth I. Heath, Howard I. Scher, Kenneth J. Pienta, Philip Kantoff[44], Johann S. de Bono[44], Mark A. Rubin[44], Peter S. Nelson[44], Levi A. Garraway[44], Charles L. Sawyers[44], Arul M. Chinnaiyan[44]

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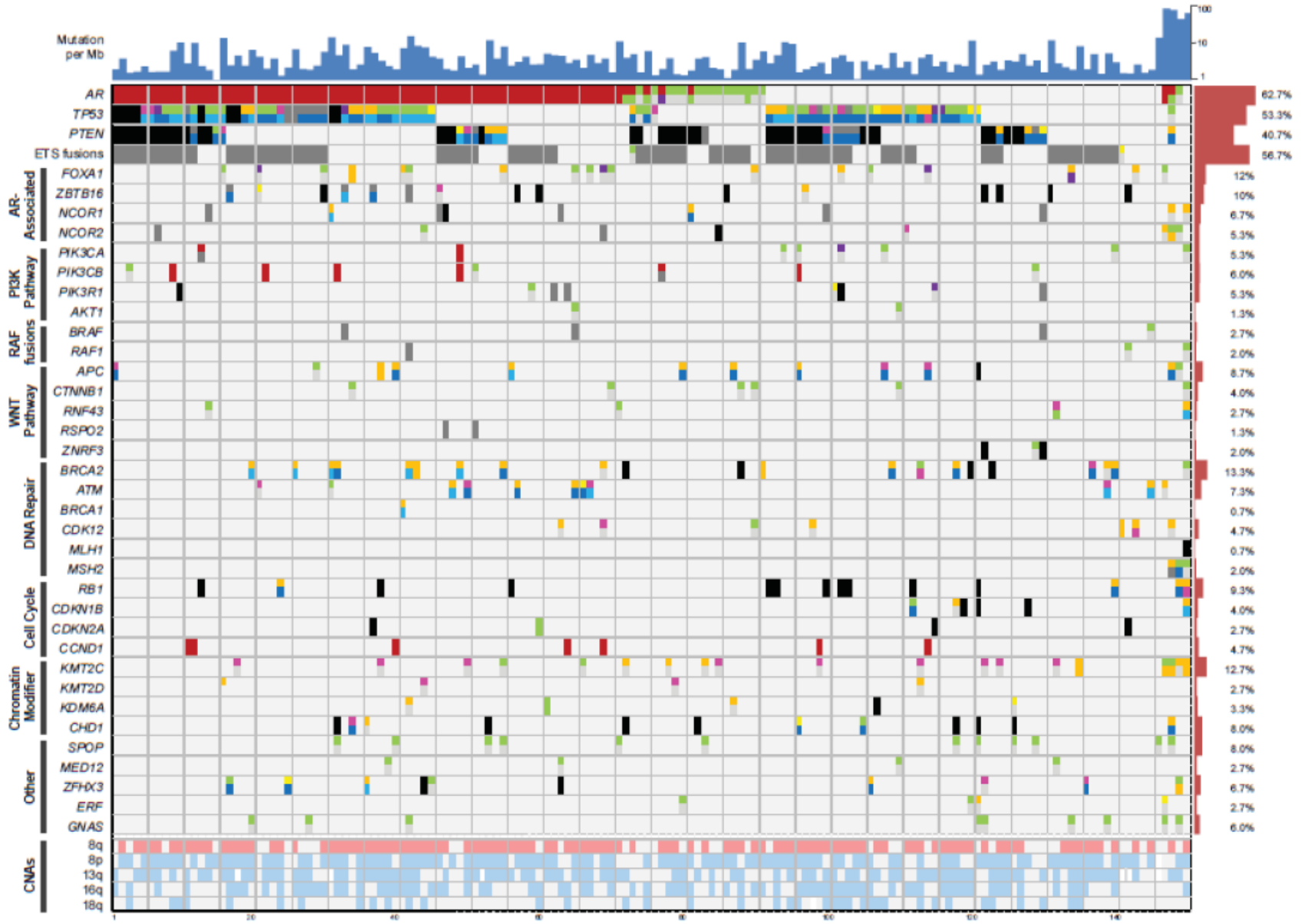
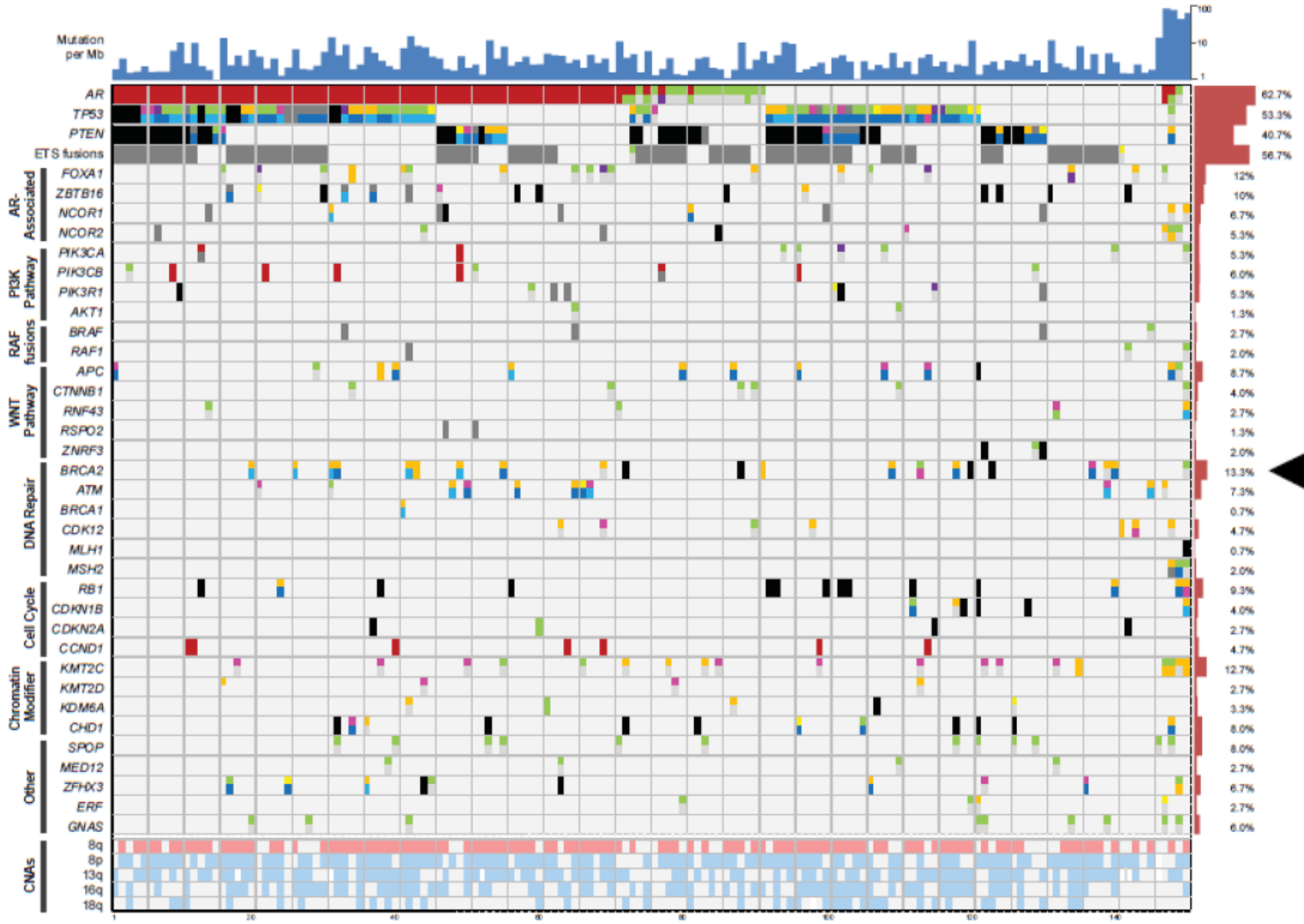
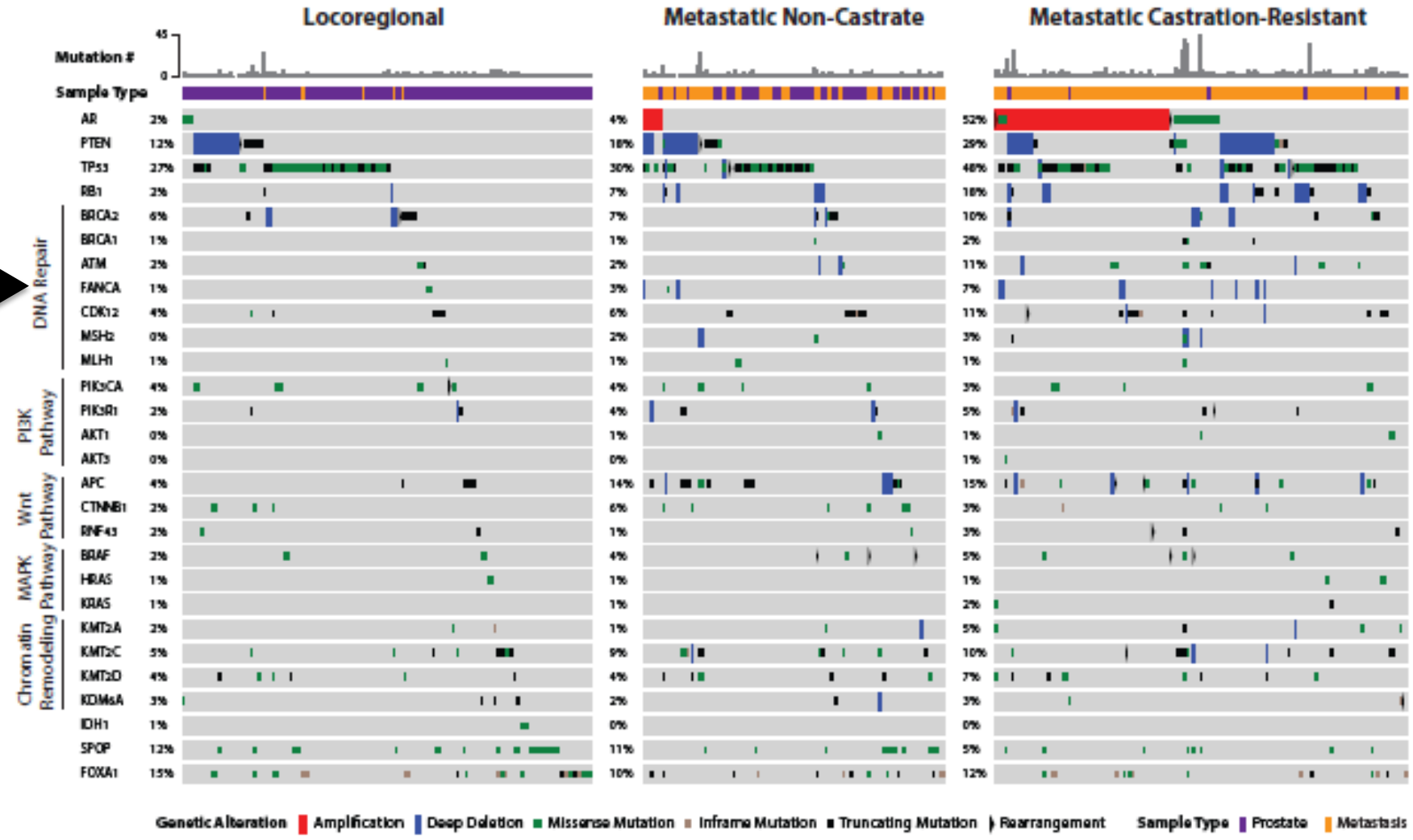



**Robinson et al Cell 2015**

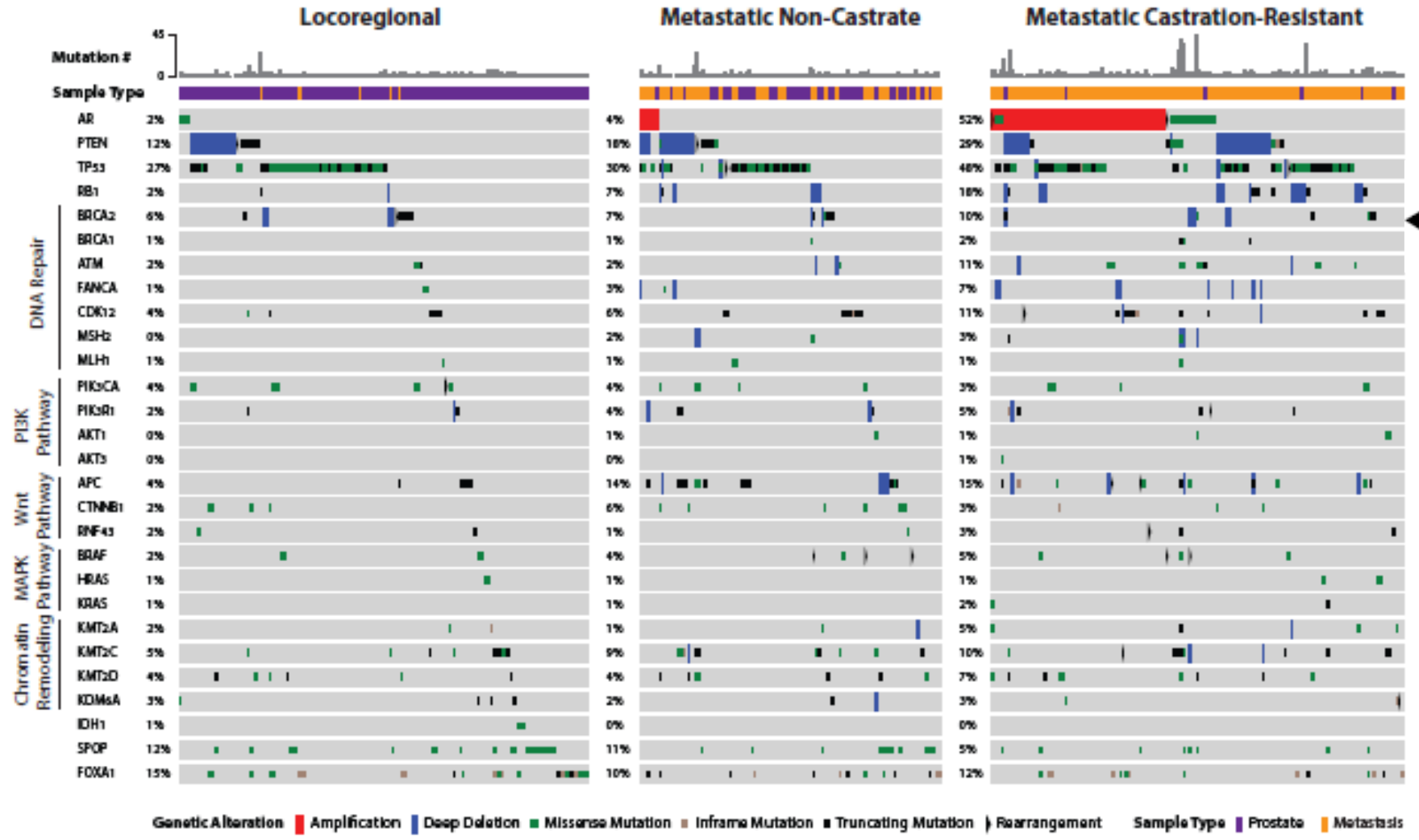

**Robinson et al Cell 2015**




**Robinson et al Cell 2015**




**Abida et al. JCO Precis Oncol. 2017**




**Abida et al. JCO Precis Oncol. 2017**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

C.C. Pritchard, J. Mateo, M.F. Walsh, N. De Sarkar, W. Abida, H. Beltran, A. Garofalo, R. Gulati, S. Carreira, R. Eeles, O. Elemento, M.A. Rubin, D. Robinson, R. Lonigro, M. Hussain, A. Chinnaiyan, J. Vinson, J. Filipenko, L. Garraway, M.-E. Taplin, S. AlDubayan, G.C. Han, M. Beightol, C. Morrissey, B. Nghiem, H.H. Cheng, B. Montgomery, T. Walsh, S. Casadei, M. Berger, L. Zhang, A. Zehir, J. Vijai, H.I. Scher, C. Sawyers, N. Schultz, P.W. Kantoff, D. Solit, M. Robson, E.M. Van Allen, K. Offit, J. de Bono, and P.S. Nelson

| | Metastatic PC (n=692) | | ExAC (without TCGA) | | Metastatic PC vs. ExAC | | Primary PC (n=499) | | Metastatic vs. Primary PC | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Gene** | Count | Freq (%) | Count | Freq (%) | RR (95% CI) | P | Count | Freq (%) | RR (95% CI) | P |
| *ATM* | 11 | 1.59% | 153 | 0.25% | 6.2 (3.1-11.1) | <0.001 | 5 | 1.00% | 1.6 (0.8-2.8) | 0.123 |
| *ATR* | 2 | 0.29% | 45 | 0.08% | 3.7 (0.4-13.3) | 0.103 | 0 | 0.00% | - | - |
| *BRCA1* | 6 | 0.87% | 133 | 0.27% | 3.2 (1.2-6.9) | 0.013 | 3 | 0.60% | 1.4 (0.5-3.1) | 0.320 |
| *BRCA2* | 37 | 5.35% | 178 | 0.30% | 17.6 (12.5-24.0) | <0.001 | 1 | 0.20% | 26.7 (18.9-36.4) | <0.001 |
| *BRIP1* | 1 | 0.18% | 116 | 0.19% | 0.9 (0.0-5.1) | 1.000 | 1 | 0.20% | 0.9 (0.0-4.9) | 1.000 |
| *CHEK2* | 10 | 1.87% | 361 | 0.64% | 2.9 (1.4-5.3) | 0.003 | 2 | 0.40% | 4.7 (2.2-8.5) | 0.000 |
| *FAM175A* | 1 | 0.18% | 57 | 0.09% | 1.9 (0.0-10.5) | 0.412 | 0 | 0.00% | - | - |
| *GEN1* | 2 | 0.46% | 47 | 0.08% | 5.8 (0.7-20.7) | 0.048 | 0 | 0.00% | - | - |
| *MRE11A* | 1 | 0.14% | 38 | 0.06% | 2.3 (0.1-12.8) | 0.353 | 1 | 0.20% | 0.7 (0.0-4.0) | 1.000 |
| *MSH2* | 1 | 0.14% | 23 | 0.04% | 3.5 (0.1-19.7) | 0.246 | 1 | 0.20% | 0.7 (0.0-4.0) | 1.000 |
| *MSH6* | 1 | 0.14% | 43 | 0.07% | 2.0 (0.1-11.2) | 0.390 | 1 | 0.20% | 0.7 (0.0-4.0) | 1.000 |
| *NBN* | 2 | 0.29% | 78 | 0.14% | 2.1 (0.3-7.6) | 0.243 | 1 | 0.20% | 1.4 (0.2-5.2) | 0.404 |
| *PALB2* | 3 | 0.43% | 78 | 0.13% | 3.3 (0.7-9.7) | 0.062 | 2 | 0.40% | 1.1 (0.2-3.1) | 0.760 |
| *PMS2* | 2 | 0.29% | 61 | 0.11% | 2.6 (0.3-9.4) | 0.180 | 1 | 0.20% | 1.4 (0.2-5.2) | 0.404 |
| *RAD51C* | 1 | 0.14% | 63 | 0.05% | 2.8 (0.1-15.4) | 0.303 | 2 | 0.40% | 0.4 (0.0-2.0) | 0.537 |
| *RAD51D* | 3 | 0.43% | 48 | 0.05% | 8.9 (1.8-25.9) | 0.005 | 1 | 0.20% | 2.2 (0.4-6.3) | 0.163 |

**Pritchard et al NEJM 2016**

REPORT

# Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

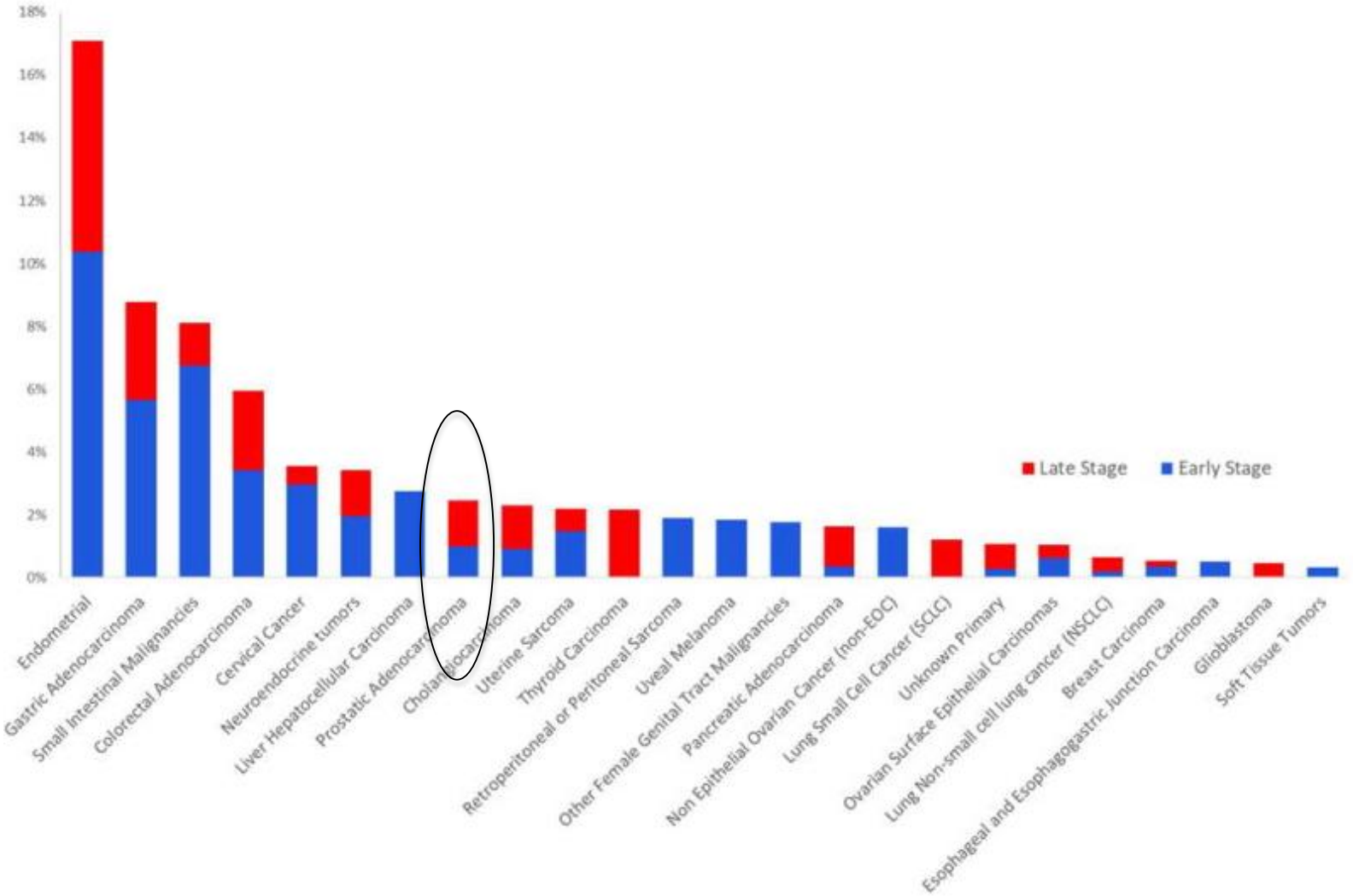
Dung T. Le[1,2,3], Jennifer N. Durham[1,2,3,*], Kellie N. Smith[1,3,*], Hao Wang[3,*], Bjarne R. Bartlett[2,4,*], Laveet...

+ See all authors and affiliations

*Science* 28 Jul 2017:
Vol. 357, Issue 6349, pp. 409-413
DOI: 10.1126/science.aan6733



# Mismatch Repair Deficiency




**Le et al. Science 2017**

Memorial Sloan Kettering Cancer Center

# Sensitivity to PARPi and Platinum

The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

# DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

Joaquin Mateo, M.D., Suzanne Carreira, Ph.D., Shahneen Sandhu, M.D., Susana Miranda, B.Sc., Helen Mossop, M.Math.Stat., Raquel Perez-Lopez, M.D., Daniel Nava Rodrigues, M.D., Dan Robinson, Ph.D., Aurelius Omlin, M.D., Nina Tunariu, M.D.Res., Gunther Boysen, Ph.D., Nuria Porta, Ph.D., Penny Flohr, B.Sc., Alexa Gillman, B.Sc., Ines Figueiredo, B.Sc., Claire Paulding, B.Sc., George Seed, M.Sc., Sunell Jain, M.D., Christy Ralph, M.D., Andrew Protheroe, M.D., Ph.D., Syed Hussain, M.D., Robert Jones, M.D., Ph.D., Tony Elliott, M.D., Ph.D., Ursula McGovern, M.D., Ph.D., Diletta Bianchini, M.D., Jane Goodall, B.Sc., Zafeiris Zafeiriou, M.D., Chris T. Williamson, Ph.D., Roberta Ferraldeschi, M.D., Ph.D., Ruth Riisnaes, F.I.B.M.S., Bernardette Ebbs, B.T.E.C., Gemma Fowler, B.Sc., Desamparados Roda, M.D., Wei Yuan, Ph.D., Yi-Mi Wu, Ph.D., Xuhong Cao, M.S., Rachel Brough, Ph.D., Helen Pemberton, Ph.D., Roger A'Hern, Ph.D., Amanda Swain, Ph.D., Lakshmi P. Kunju, M.D., Rosalind Eeles, M.D., Ph.D., Gerhardt Attard, M.D., Ph.D., Christopher J. Lord, Ph.D., Alan Ashworth, Ph.D., Mark A. Rubin, M.D., Karen E. Knudsen, Ph.D., Felix Y. Feng, M.D., Ph.D., Arul M. Chinnaiyan, M.D., Ph.D., Emma Hall, Ph.D., and Johann S. de Bono, M.B., Ch.B., Ph.D.

N Engl J Med 2015; 373:1697-1708 | October 29, 2015 | DOI: 10.1056/NEJMoa1506859

# Olaparib in mCRPC

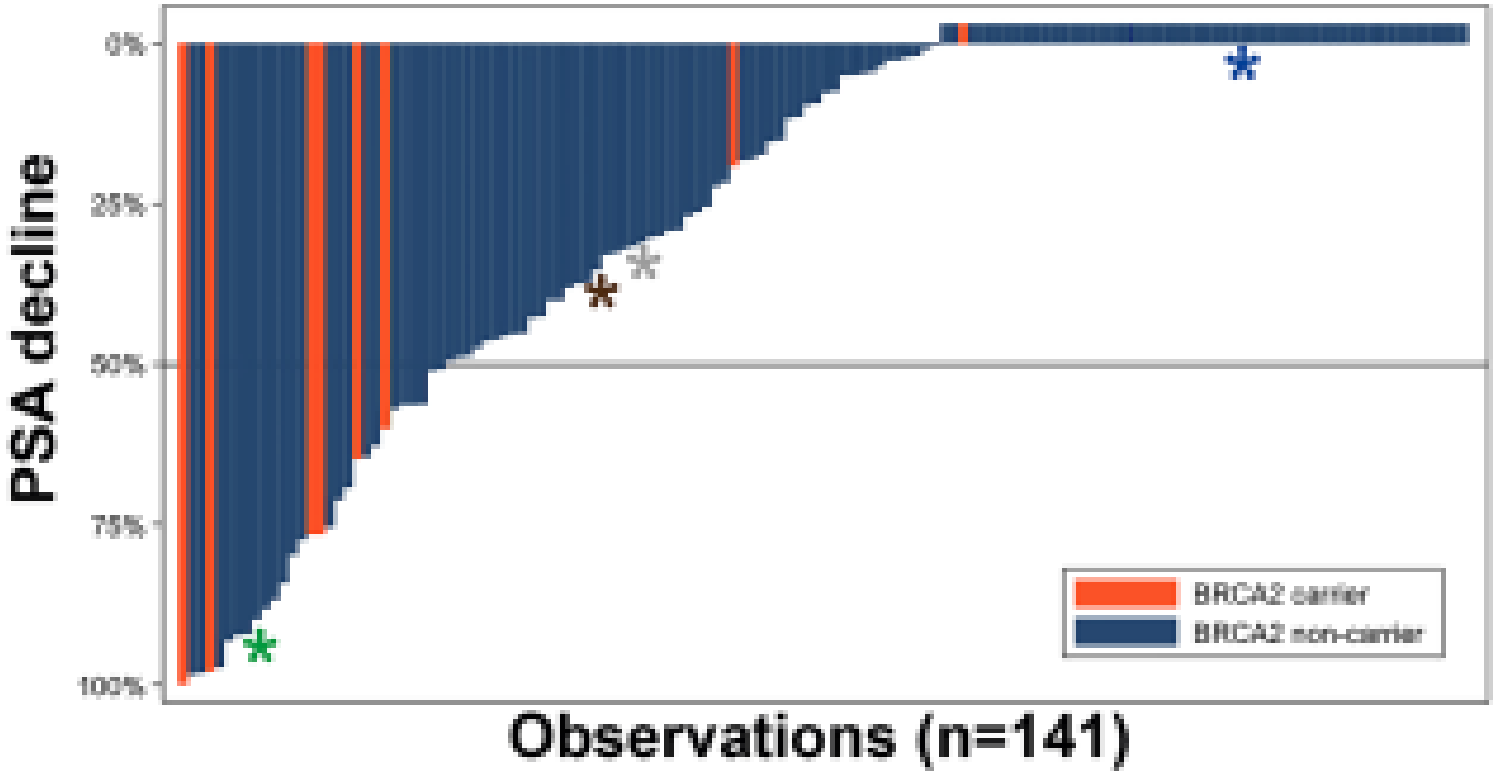
- 50 patients with mCRPC treated with Olaparib;
- Of the 16 patients who responded to Olaparib, 14 were found to have mutations in known DNA damage-repair genes, while only 2 of the 33 non-responders had mutations in any of these genes;
- Altered DNA damage-repair genes identified in the tumors of responders included BRCA2, BRCA1, ATM, FANCA, CHEK2, PALB2, HDAC2, MRE11, and NBN; and
- Germline or somatic alteration of DNA repair was 94% predictive of response.

**Mateo et al NEJM 2015**

# January 2016-FDA Grants Olaparib Breakthrough Designation in mCRPC

Olaparib received an FDA breakthrough therapy designation as a treatment for patients with BRCA1/2 or ATM-mutated mCRPC in those who have received a prior taxane-based chemotherapy and at least either hormonal agent enzalutamide or abiraterone acetate.

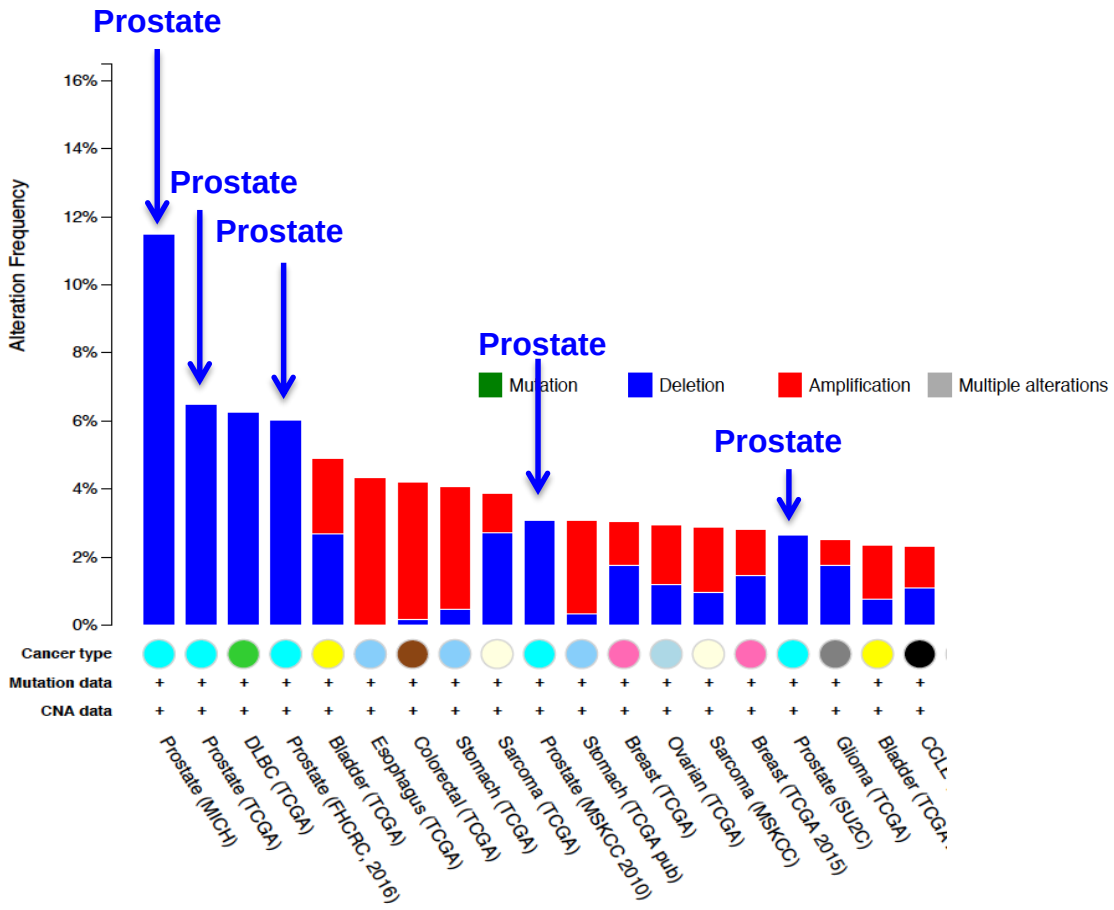
# BRCA2 germline mutations confer sensitivity to carboplatin




Pomerantz et al Cancer 2017

# BRCA2 is frequently deleted (homozygous and heterozygous) in early prostate cancer

## BRCA 2 CNA (Pan cancer)



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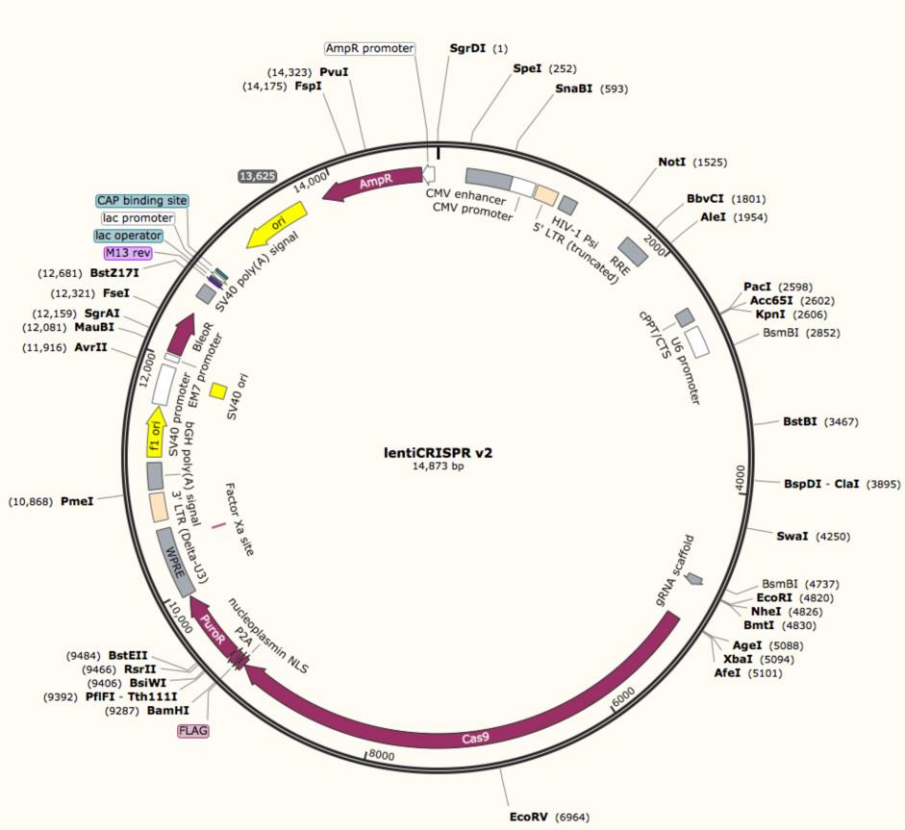
# BRCA2 loss induces an aggressive castration resistant phenotype in prostate cancer cell line LNCaP

# CRISPR out of BRCA2 in LNCaP cells

## A Lenti CRISPR construct containing both guide-RNA and CAS9 was used for deleting BRCA2 in LNCaP cells



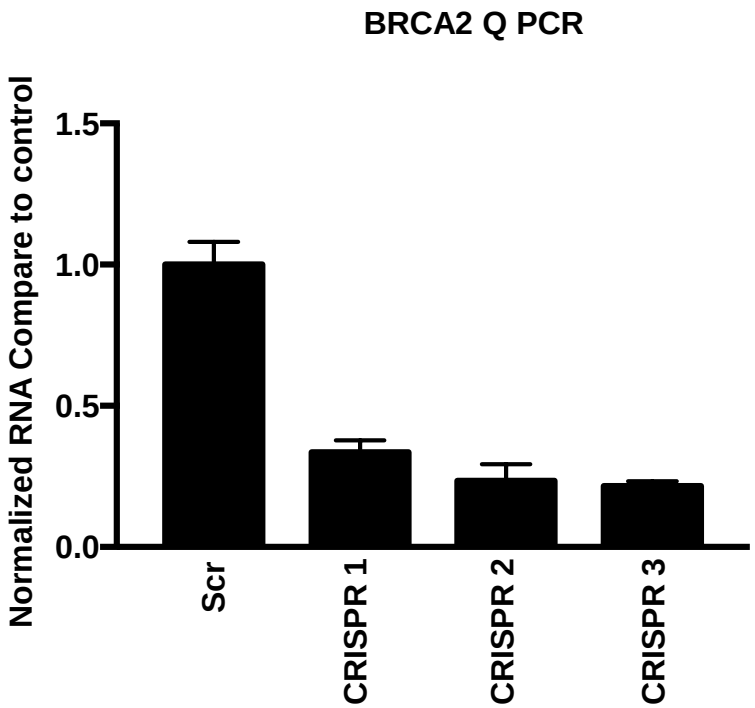

**Lentivirus** →

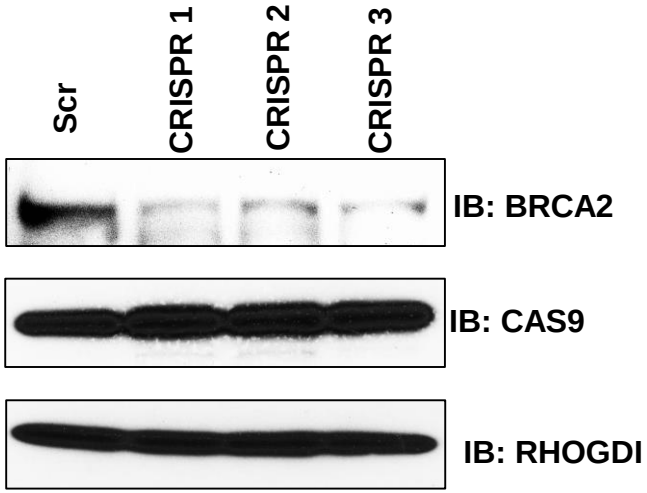
**Infection of LNCaP Cells**

**3 Guide RNAs had been designed**

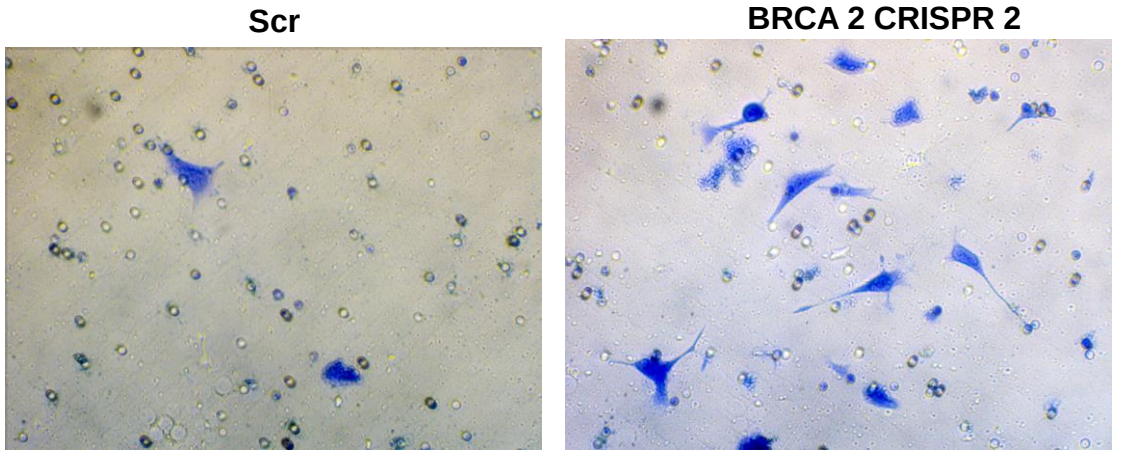
**Infected cells were selected by puromycin selection**

# CRISPR deleted BRCA2 in LNCaP

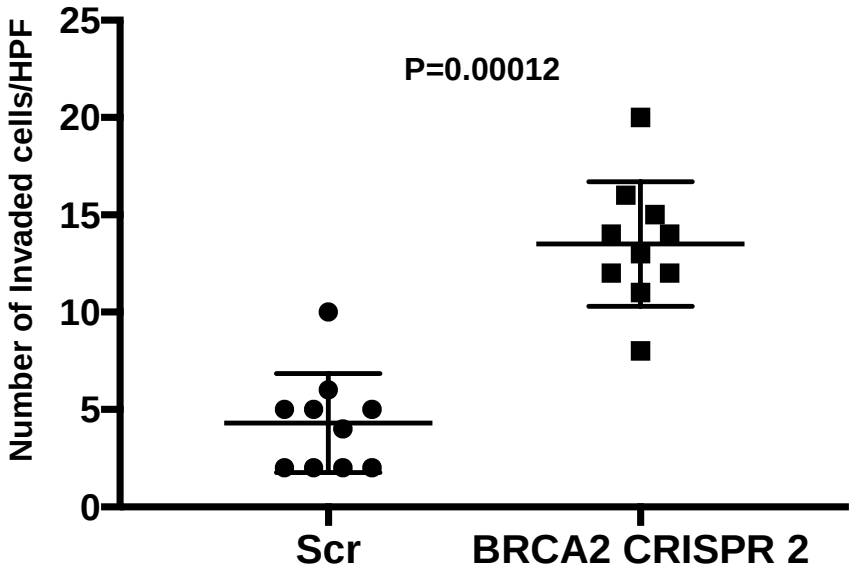


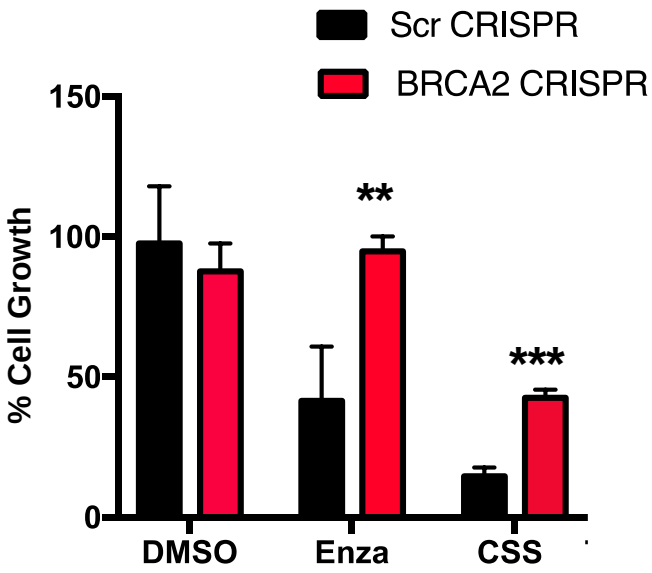
# Increased Matrigel invasiveness of BRCA2 deleted cells



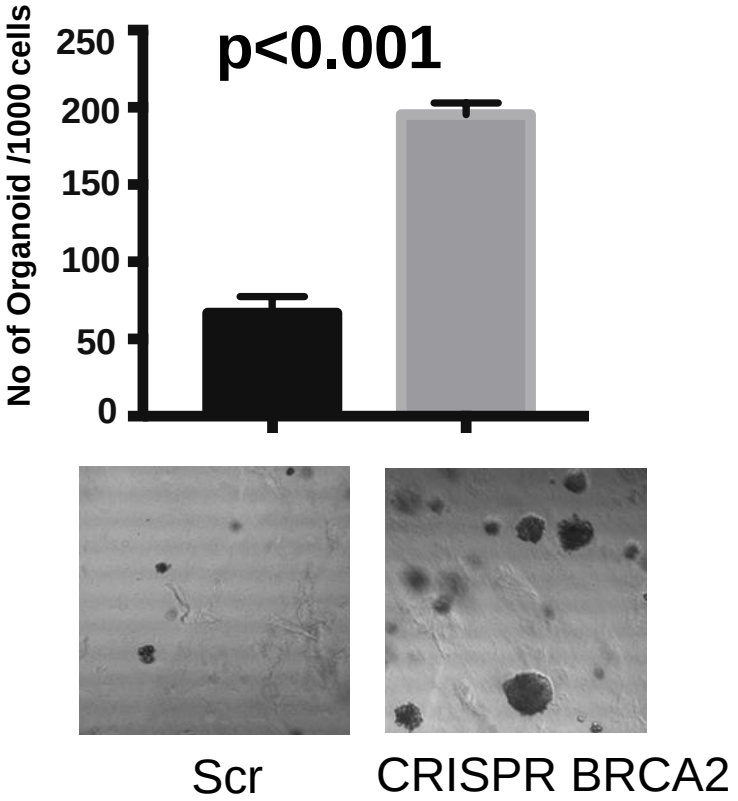

Invaded cells/ 24 hr



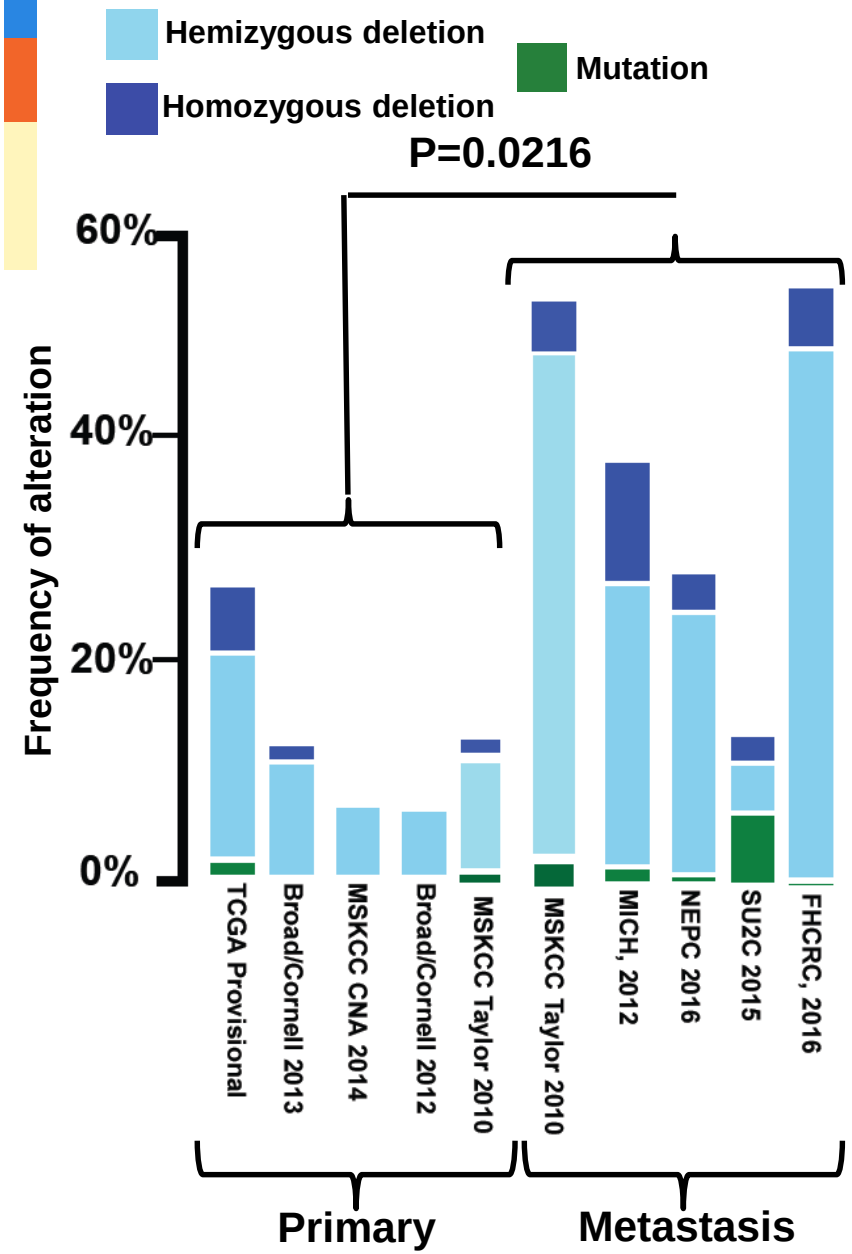
# BRCA2 deleted LNCaP cells are enzalutamide resistant and can grow in androgen deprived conditions but are PARPi sensitive

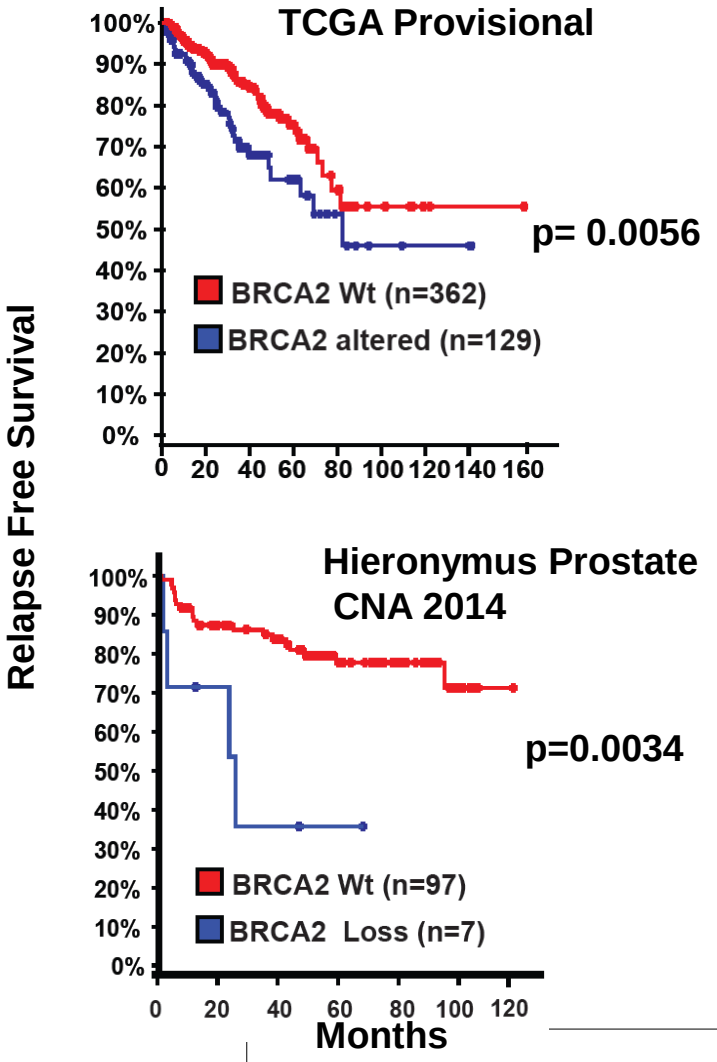



3D organoid in androgen deprived condition

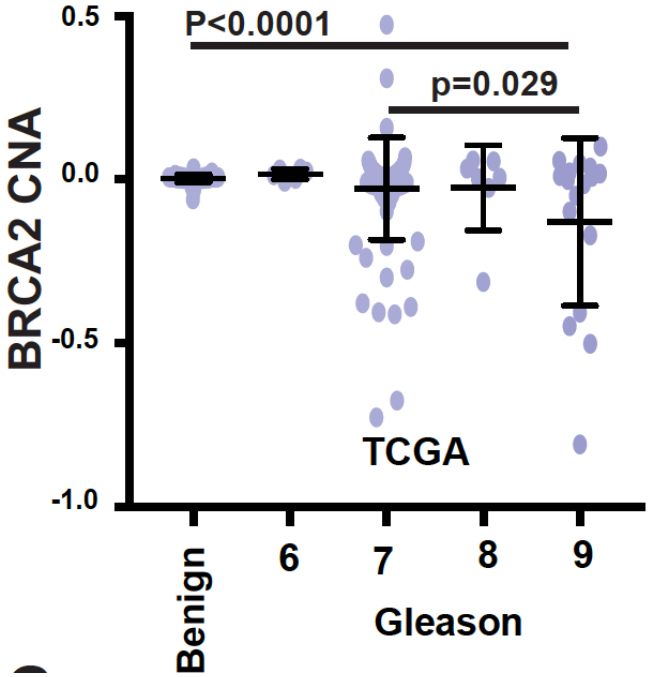


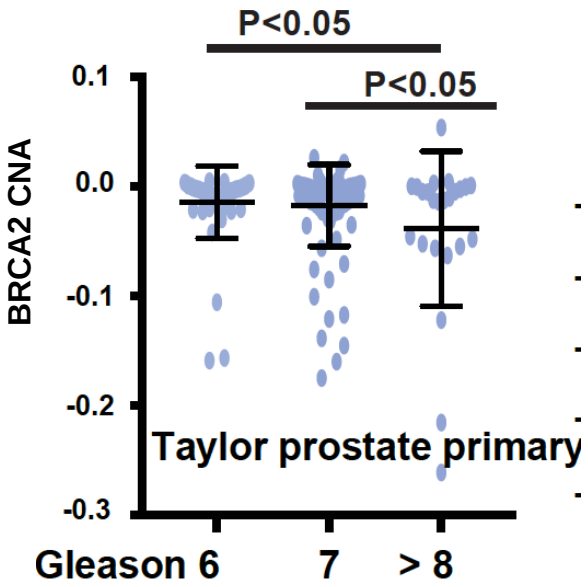
# Frequent hemizygous deletions of BRCA2 in primary as well as metastatic PC

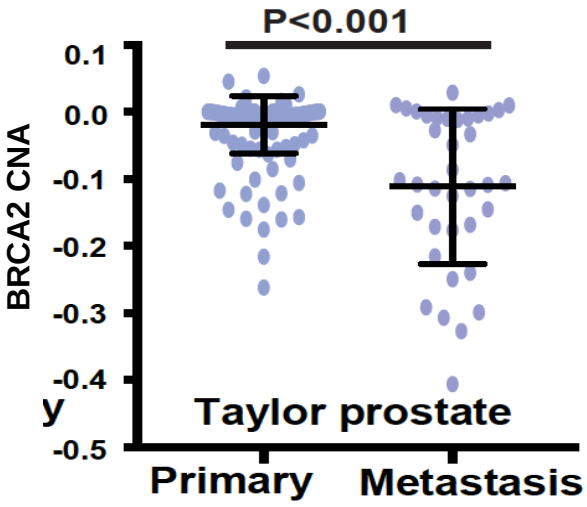


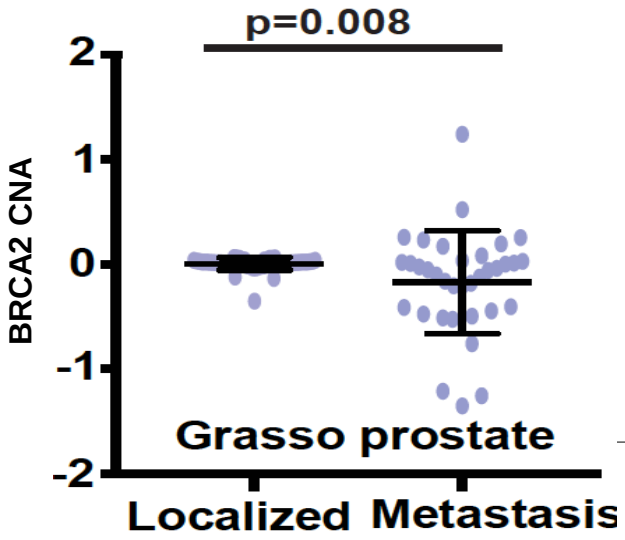



# BRCA2 copy number loss is associated with Gleason grade and metastatic progression of PC



# Do DNA Repair Abnormalities alter sensitivity to ADT

ELSEVIER

European Urology

Volume 72, Issue 1, July 2017, Pages 34-42

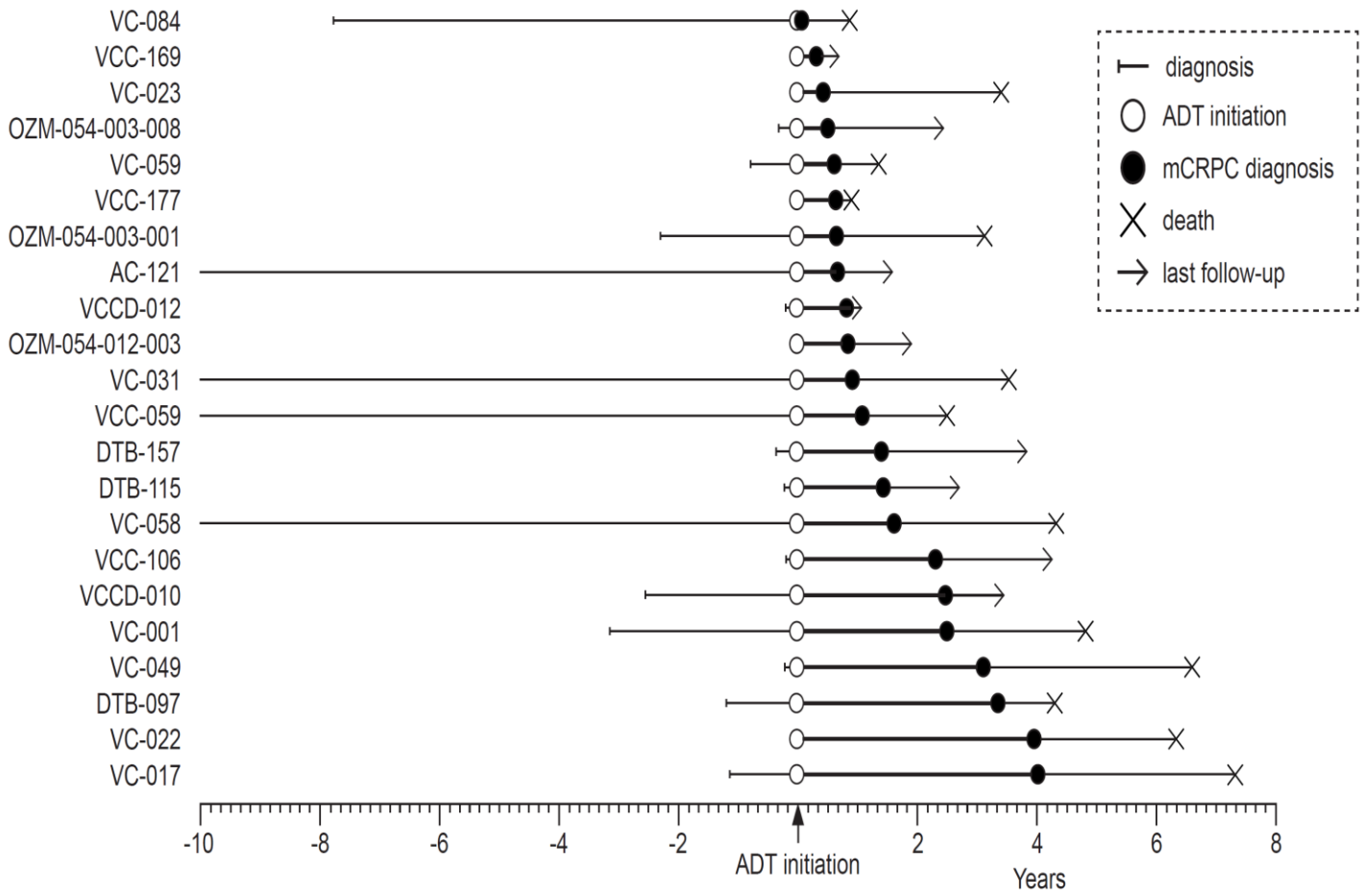
Platinum Priority – Prostate Cancer

*Editorial by Emmanuel S. Antonarakis on pp. 43–44 of this issue*

# Treatment Outcomes and Tumor Loss of Heterozygosity in Germline DNA Repair–deficient Prostate Cancer

Matti Annala [a, b, †], Werner J. Struss [a, †], Evan W. Warner [a], Kevin Beja [a], Gillian Vandekerkhove [a], Amanda Wong [a], Daniel Khalaf [c], Irma-Liisa Seppälä [b], Alan So [a], Gregory Lo [d], Rahul Aggarwal [e], Eric J. Small [e], Matti Nykter [b], Martin E. Gleave [a], Kim N. Chi [a, c, ‡], Alexander W. Wyatt [a, ‡]

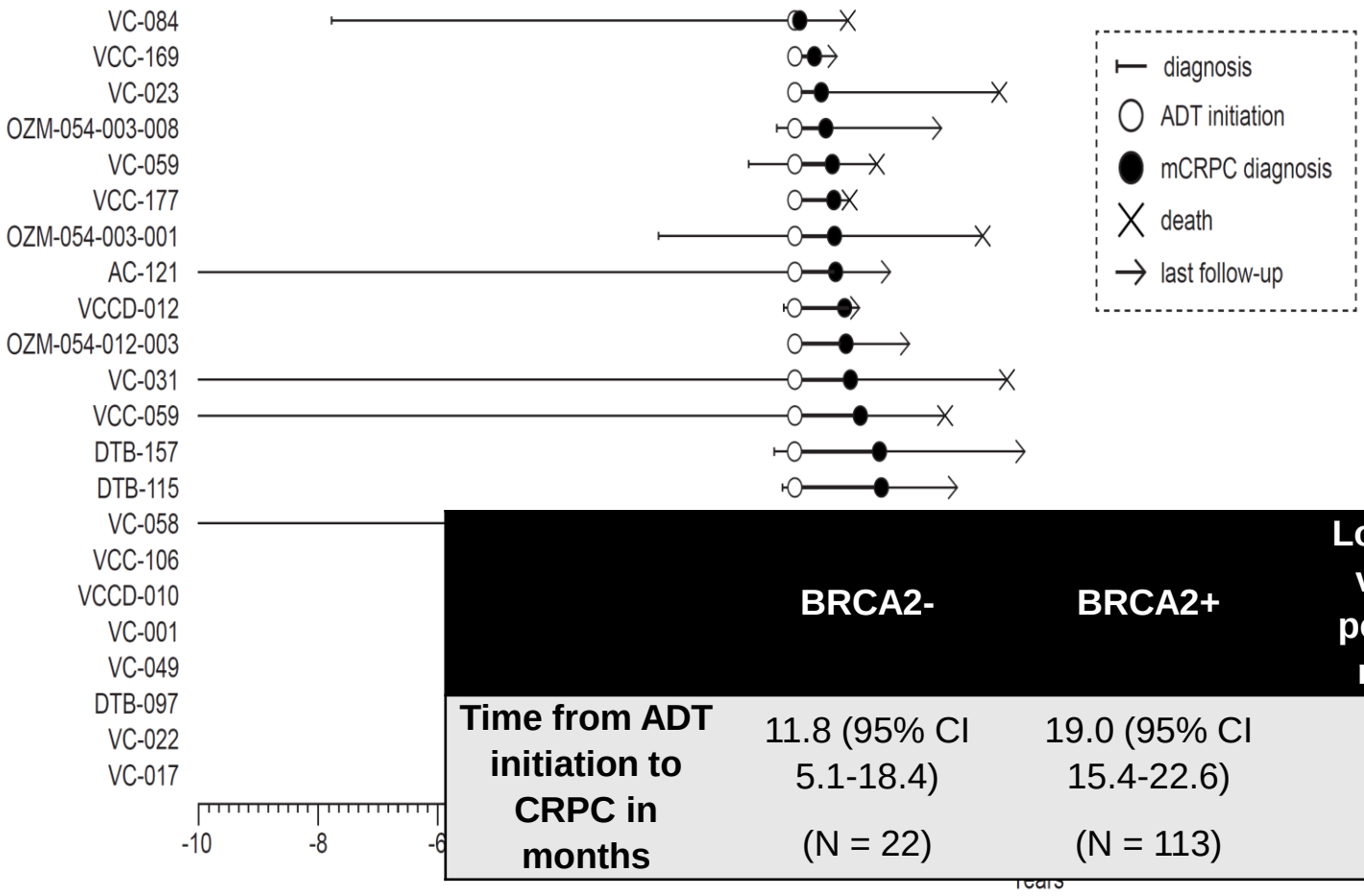
# ATTENUATED RESPONSE TO PRIMARY ANDROGEN DEPRIVATION THERAPY




The median time from ADT initiation to castration-resistance was only **11.8 months** (95% CI 5.1-18.4).

**Annala et al Eur Urol 2017**

# ATTENUATED RESPONSE TO PRIMARY ANDROGEN DEPRIVATION THERAPY




| | BRCA2- | BRCA2+ | Log-rank p-value for positive vs negative |
|---|---|---|---|
| **Time from ADT initiation to CRPC in months** | 11.8 (95% CI 5.1-18.4)<br>(N = 22) | 19.0 (95% CI 15.4-22.6)<br>(N = 113) | 0.031 |

The median time from ADT initiation to castration-resistance was only **11.8 months** (95% CI 5.1-18.4).

**Annala et al Eur Urol 2017**

European Urology

Available online 8 February 2018

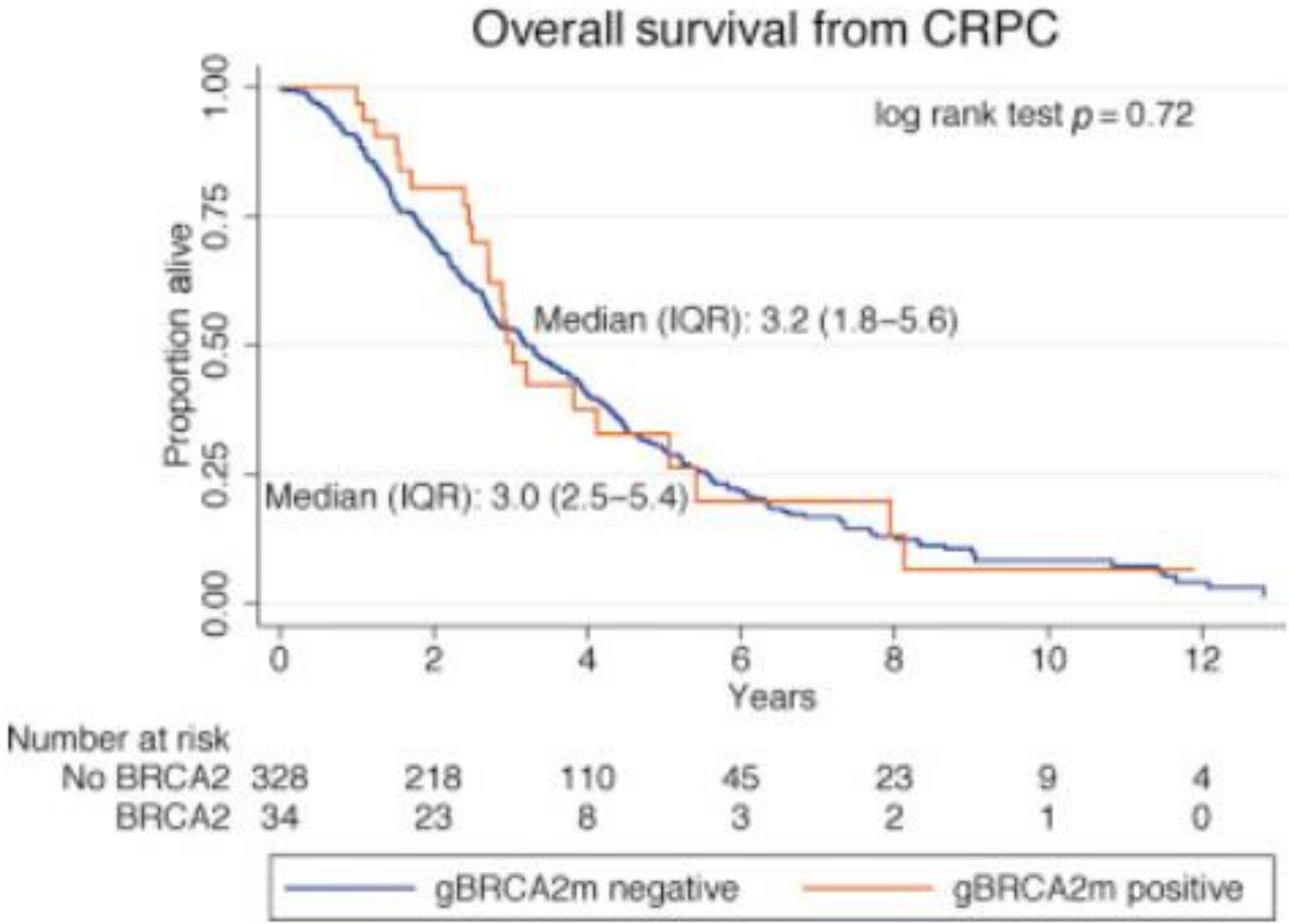
In Press, Corrected Proof

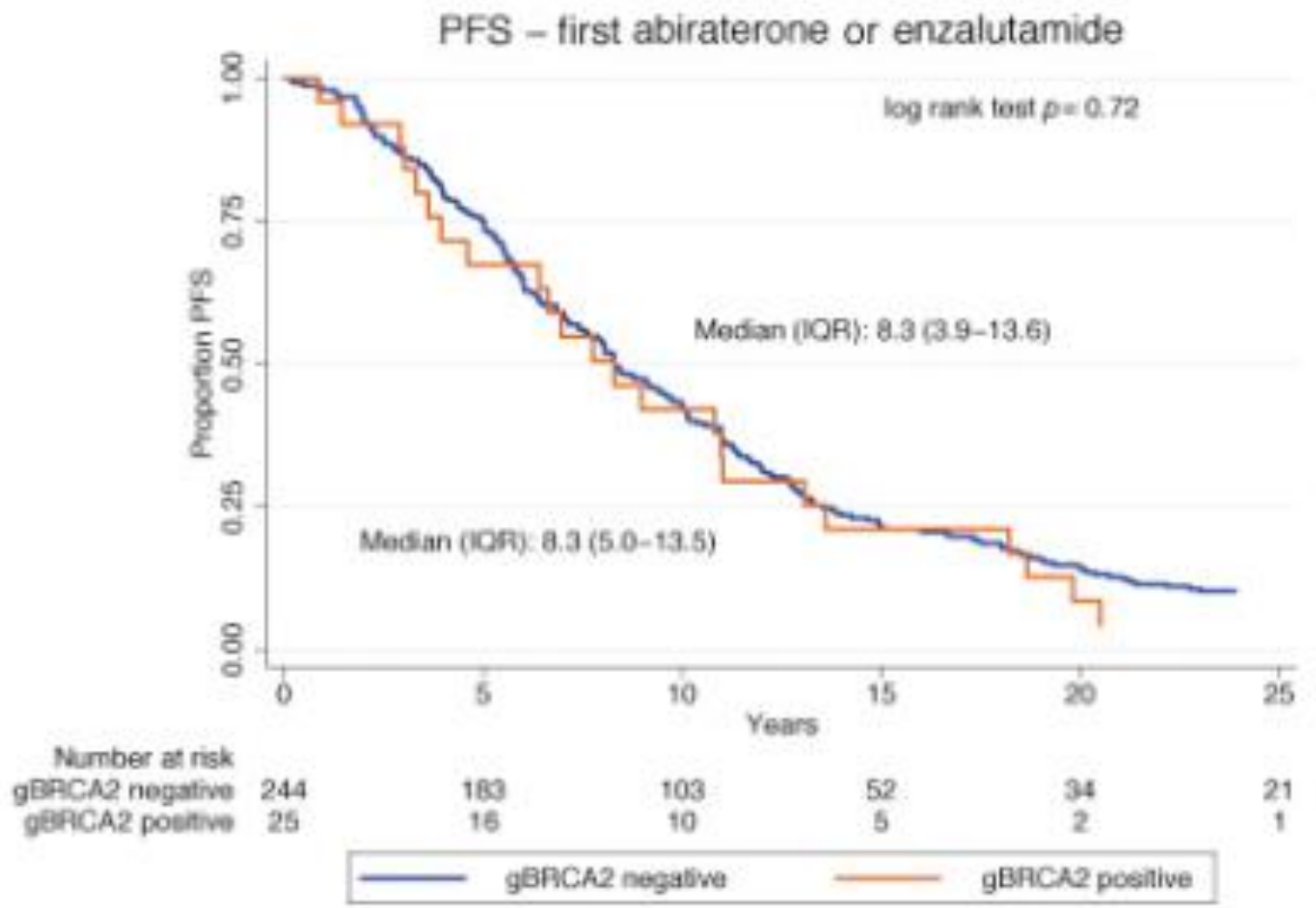
Platinum Priority – Prostate Cancer

*Editorial by XXX on pp. x–y of this issue*

# Clinical Outcome of Prostate Cancer Patients with Germline DNA Repair Mutations: Retrospective Analysis from an International Study

Joaquin Mateo [a, b, c, †], Heather H. Cheng [d, e, †], Himisha Beltran [f, †], David Dolling [a], Wen Xu [g], Colin C. Pritchard [d, e], Helen Mossop [a], Pasquale Rescigno [a, b], Raquel Perez-Lopez [a, b, c], Verena Sailer [f], Michael Kolinsky [a, b], Ada Balasopoulou [a], Claudia Bertan [a], David M. Nanus [f], Scott T. Tagawa [f], Heather Thorne [g, h], Bruce Montgomery [d, e], Suzanne Carreira [a] … Johann S. de Bono [a, b, ‡]


Overall survival from CRPC
log rank test p = 0.72
Median (IQR): 3.2 (1.8–5.6)
Median (IQR): 3.0 (2.5–5.4)
Proportion alive
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
12
Years
Number at risk
No BRCA2 328 218 110 45 23 9 4
BRCA2 34 23 8 3 2 1 0
gBRCA2m negative
gBRCA2m positive


PFS – first abiraterone or enzalutamide
log rank test p = 0.72
Median (IQR): 8.3 (3.9–13.6)
Median (IQR): 8.3 (5.0–13.5)
Proportion PFS
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
25
Years
Number at risk
gBRCA2 negative 244 183 103 52 34 21
gBRCA2 positive 25 16 10 5 2 1
gBRCA2 negative
gBRCA2 positive

# A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

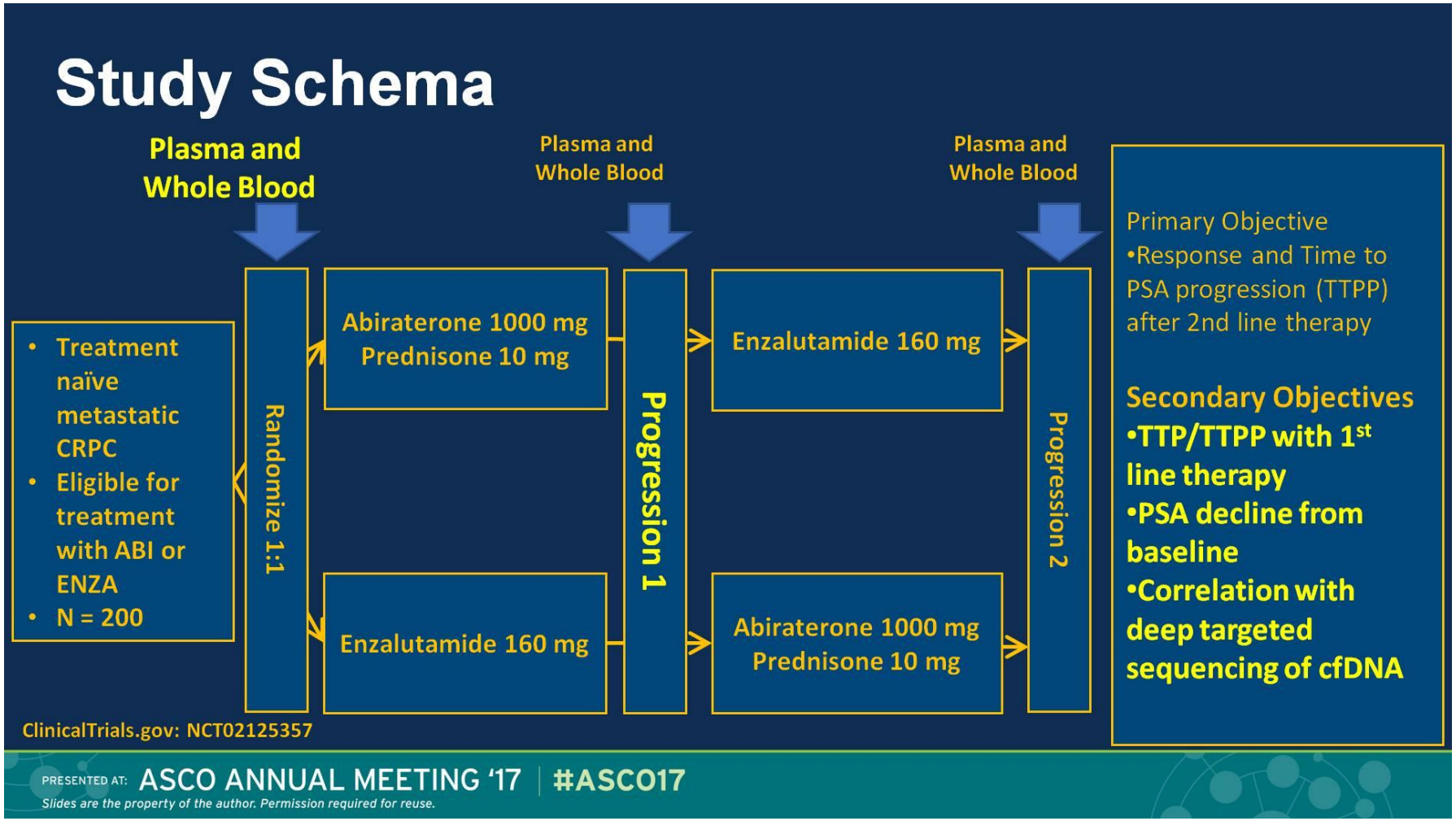
Kim N. Chi, Matti Annala, Katherine Sunderland, Daniel Khalaf, Daygen Finch, Conrad D. Oja, Joanna Vergidis, Muhammad Zulfiqar, Kevin Beja, Gillian Vandekerkhove, Martin Gleave, Alexander W. Wyatt

British Columbia Cancer Agency, Vancouver, BC; Institute of Biosciences and Medical Technology, Tampere, Finland; BC Cancer Agency - Vancouver Centre, Vancouver, BC; BC Cancer Agency - Centre for the Southern Interior, Kelowna, BC; British Columbia Cancer Agency, Fraser Valley Centre, Vancouver, BC; British Columbia Cancer Agency, Vancouver Island Centre, Victoria, BC; BC Cancer Agency, Abbotsford, BC; Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC; Vancouver Prostate Centre, University of British Columbia, Vancouver, BC

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17

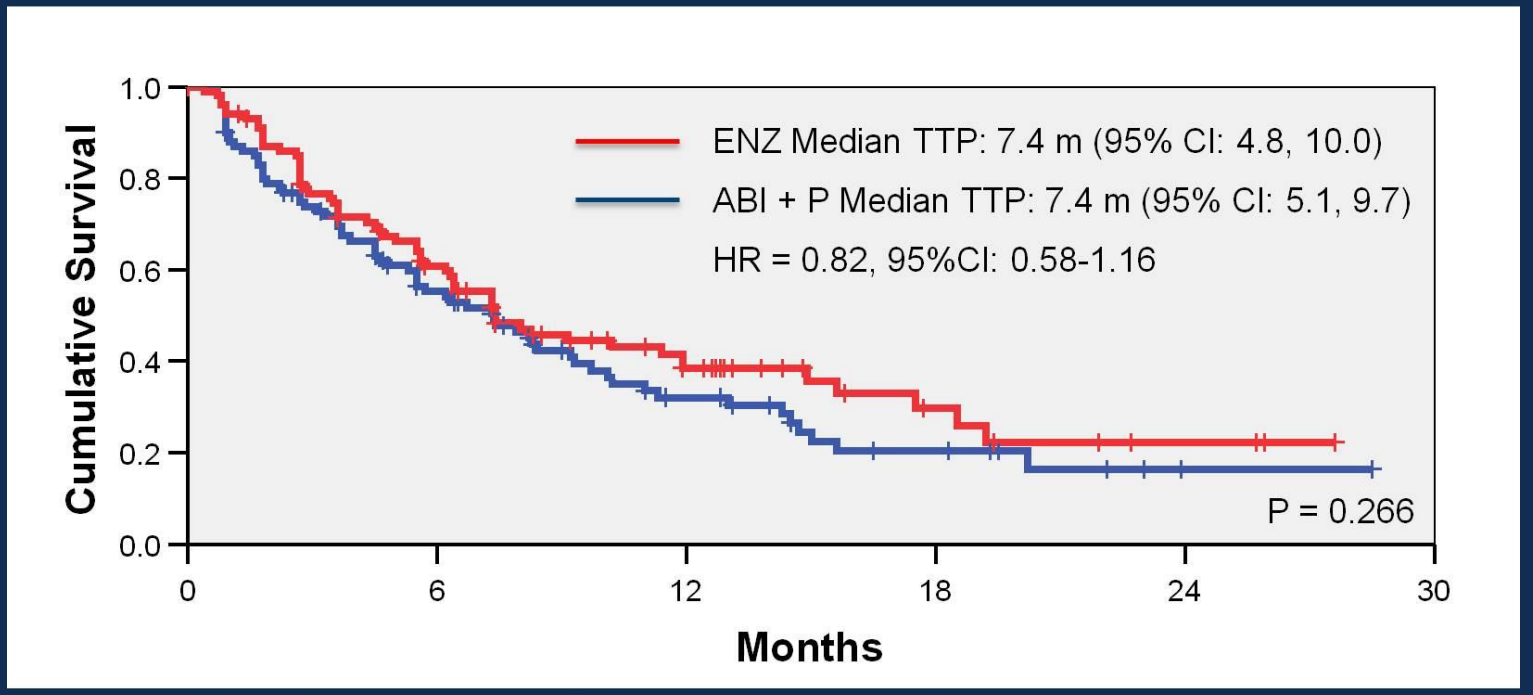


Chi et al Canc Disc 2018




Chi et al Canc Disc 2018

# Time to Progression




*First of confirmed PSA progression (PCWG3), clinical or radiological progression, or death from disease




Chi et al Canc Disc 2018

# Genomic Correlates with TTP

| Genomic Alteration | Median TTP Positive vs Negative* (months) | Univariate | | Multivariate*** | |
|---|---|---|---|---|---|
| | | HR | P-value | HR | P-value |
| **BRCA2/ATM truncating mutation** | **1.8 vs 8.0** | **6.14 (3.35-11.26)** | **<0.001** | **5.34 (2.84-10.03)** | **<0.001** |
| **TP53 inactivation**** | **3.3 vs 10.2** | **2.78 (1.92-4.03)** | **<0.001** | **2.21 (1.38-3.55)** | **0.001** |
| **PI3K pathway** | **3.3 vs 10.4** | **2.73 (1.91-3.90)** | **<0.001** | **1.95 (1.31-2.90)** | **<0.001** |
| **AR amplification** | **5.0 vs 9.3** | **2.05 (1.43-2.93)** | **<0.001** | 1.29 (0.85-2.09) | 0.271 |
| **RB1 inactivation**** | **3.6 vs 8.2** | **2.03 (1.36-3.04)** | **<0.001** | 1.45 (0.95-2.21) | 0.08 |
| SPOP mutation | 7.3 vs 7.4 | 1.00 (0.51-1.97) | 1.00 | | |
| AR mutation | 6.2 vs 7.4 | 1.02 (0.53-1.95) | 0.95 | | |

Includes patients without detectable ctDNA; ** Mutation, deletion, or rearrangement
*** MVA includes trial arm, presence of quantifiable ctDNA, and clinical prognostic factors (LDH, ALP, Visceral Mets, ECOG PS)

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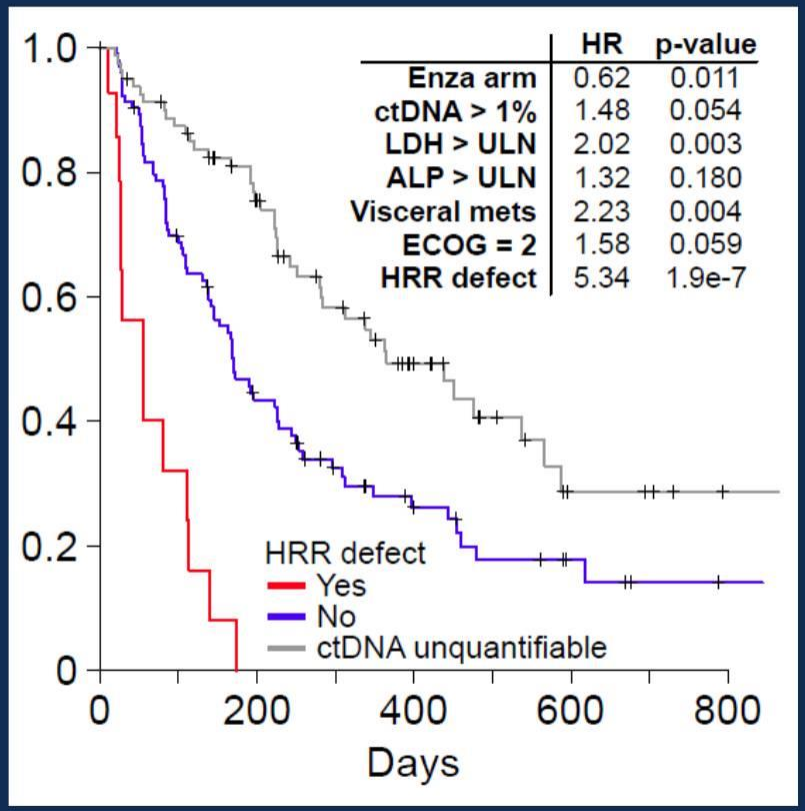
# *BRCA2/ATM*

- BRCA2 or ATM truncating mutations or rearrangements
  - Somatic: detected in 6 of 115 (5.2%) Germline: detected in 8 of 202 (4.0%)
  - 9/14 progressed within 12 weeks
- Mono-allelic BRCA2 or ATM deletion in 22 patients
  - No difference in TTP (P = 0.09)

Time to Progression







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# Summary

1. DNA repair abnormalities are common in men with mCRPC
2. BRCA2 germline and somatic are the most common and frequently homozygous and heterozygous deletions
3. CRISPR mediated loss of BRCA2 in LNCaP induces an aggressive phenotype including castration resistance.
4. Clinically, associated with aggressive phenotype
5. Conflicting data regarding BRCA2 loss and resistance to ADT
6. Clinically BRCA2 mutations associated with PARP and platinum sensitivity

# Questions

1. What are the implications for screening?
2. Should low risk patients with 3+3 or 3+4 with DNA repair abnormalities go on AS
3. Should those individuals with localized disease who have DDR alterations be treated differently ie (XRT rather than RP?) or addition of PARPi or platinum?