# MAMTA PARIKH, MD, MS

## CHALLENGING CASE #2: GU CANCER
## &
## STATE OF THE ART: CASTRATION RESISTANT PROSTATE CANCER

NO RELEVANT FINANCIAL RELATIONSHIPS IN THE PAST TWELVE MONTHS BY PRESENTER OR SPOUSE/PARTNER.

THE SPEAKER WILL DIRECTLY DISCLOSURE THE USE OF PRODUCTS FOR WHICH ARE NOT LABELED (E.G., OFF LABEL USE) OR IF THE PRODUCT IS STILL INVESTIGATIONAL.

The Medical Educator Consortium

14th Annual California Cancer Conference Consortium
August 10-12, 2018

# Castration Resistant Prostate Cancer: State of the Art 2018

Mamta Parikh, MD,MS
UC Davis Comprehensive Cancer Center

# Outline

- Where we were
- M0 CRPC therapy
- Immunotherapeutic approaches
- DNA repair pathway- combinations
- Distinct gene signatures- t-SCNC

# State of the Art 2017: mCRPC

- Chemotherapy
  - Docetaxel
  - Cabazitaxel
- Anti-androgen agents
  - Abiraterone + prednisone
  - Enzalutamide
- Radium-223
- Immunotherapy
  - Sipuleucel-T

# What about M0 CRPC?

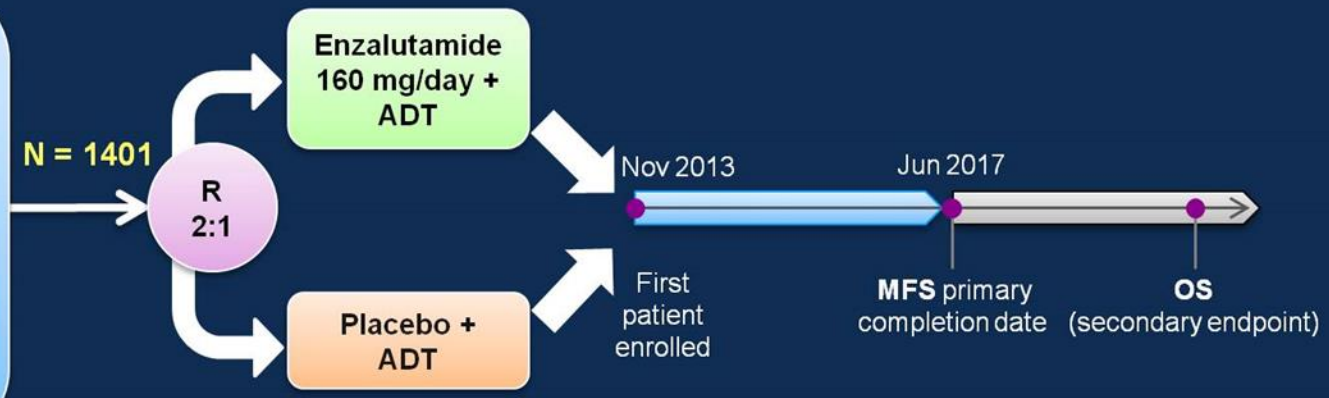
- 2017 ASCO guidelines
  - ‘no data to support the use of second-line hormonal therapies for chemotherapy-naïve men with M0 CRPC who are at **low risk** of developing metastases’
  - ‘for chemotherapy-naïve patients at high risk of developing metastases (rapid PSA doubling time or velocity), second-line hormonal therapies that lower PSA values or slow rate of increase may be offered, preferably in a clinical trial setting where available, after discussion with patient about limited scientific evidence, potential harms, benefits, cost, and patient preferences’

# Enzalutamide in M0 CRPC

## PROSPER Study Design

**Key Eligibility Criteria**
- M0 CRPC (central review)
- Rising PSA despite castrate testosterone level (≤ 50 ng/dL)
- Baseline PSA ≥ 2 ng/mL
- PSA doubling time ≤ 10 months

**Stratification Factors**
- PSA doubling time (< 6 months vs 6-10 months)
- Baseline use of bone-targeted agent (yes vs no)




**Primary endpoint**
- MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation)

**Statistical Design:**
- Target difference in Kaplan-Meier estimated median MFS of 9 months (24 months vs 33 months)
- Target of 440 events provides 90% power to detect a target HR of 0.72

**Secondary endpoints**
- Safety
- Time to PSA progression
- Time to use of new antineoplastic therapy
- OS
- PSA response
- Quality of life

Abbreviations: ADT, androgen deprivation therapy; HR, hazard ratio; R, randomization.

# Enzalutamide in M0 CRPC

## Primary Endpoint: MFS

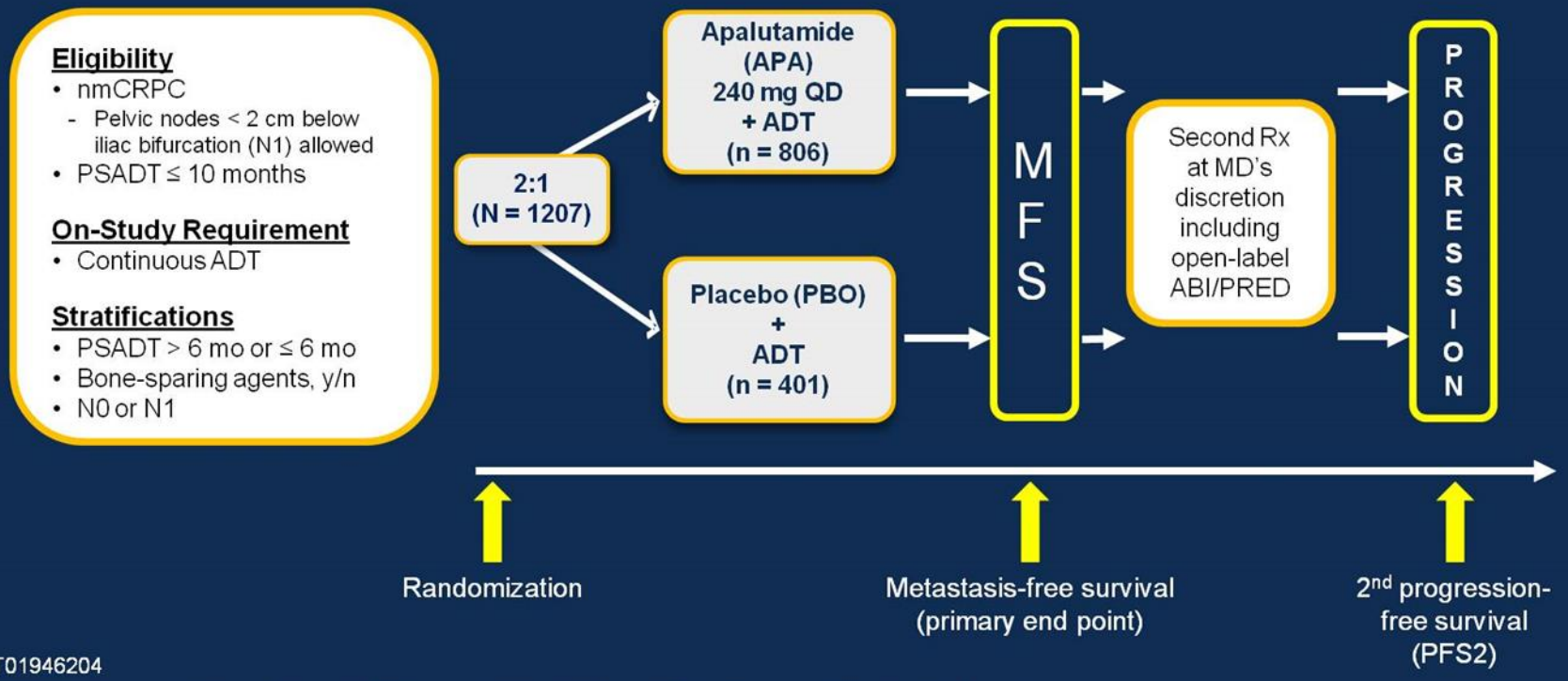

| | ENZA + ADT (n = 933) | PBO + ADT (n = 468) |
|---|---|---|
| Median (95% CI), mo | 36.6 (33.1-NR) | 14.7 (14.2-15.0) |
| HR (95% CI) | 0.29 (0.24-0.35) | |
| *P* value | < .0001 | |

| No. at risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ENZA + ADT | 933 | 865 | 759 | 637 | 528 | 431 | 418 | 328 | 237 | 159 | 87 | 77 | 31 | 4 | 0 |
| PBO + ADT | 468 | 420 | 296 | 212 | 157 | 105 | 98 | 64 | 49 | 31 | 16 | 11 | 5 | 1 | 0 |

- Median MFS was ≈ 22 months longer with enzalutamide than with placebo (71% reduction in relative risk of radiographic progression or death)

Abbreviations: CI, confidence interval; ENZA, enzalutamide; NR, not reached; PBO, placebo.

# Apalutamide in M0 CRPC



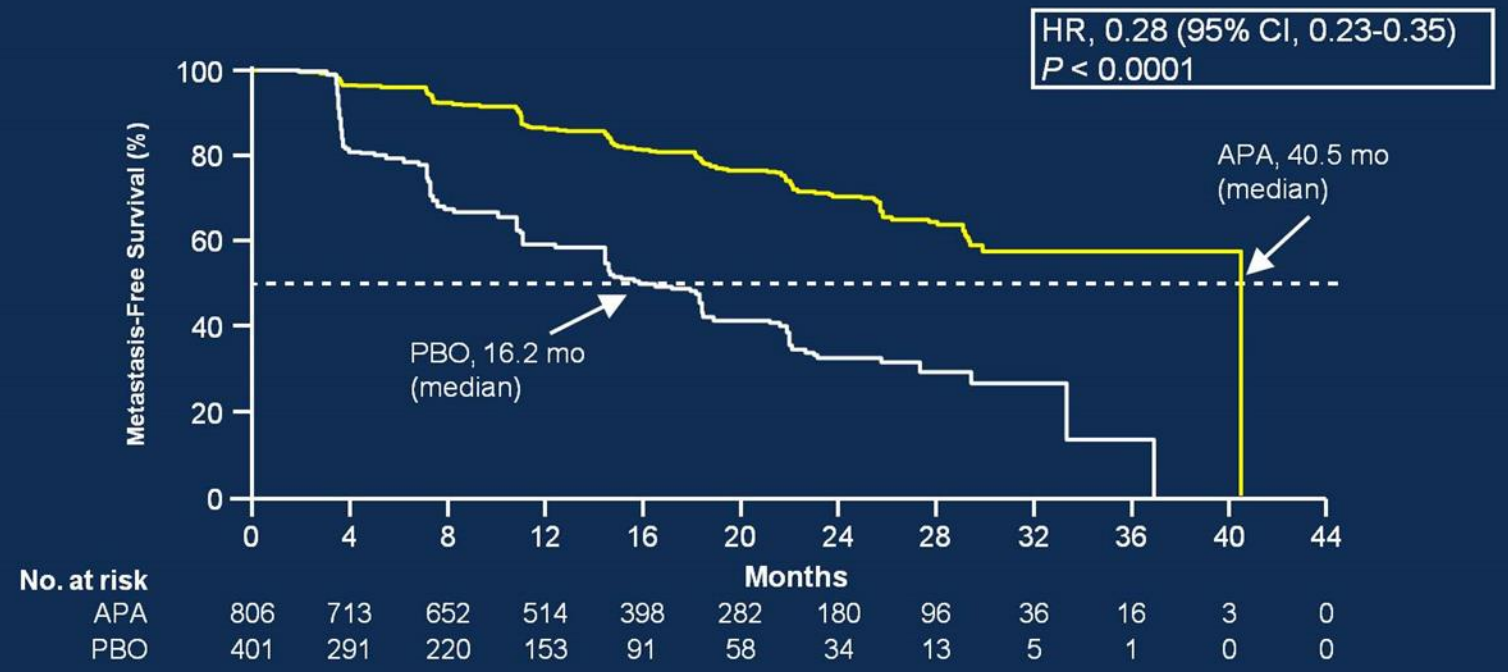

NCT01946204

ABI/PRED, abiraterone acetate plus prednisone; nmCPRC, nonmetastatic castration-resistant prostate cancer; MFS, metastasis-free survival.

# Apalutamide in M0 CRPC

## Primary End Point: Metastasis-Free Survival

72% risk reduction of distant progression or death

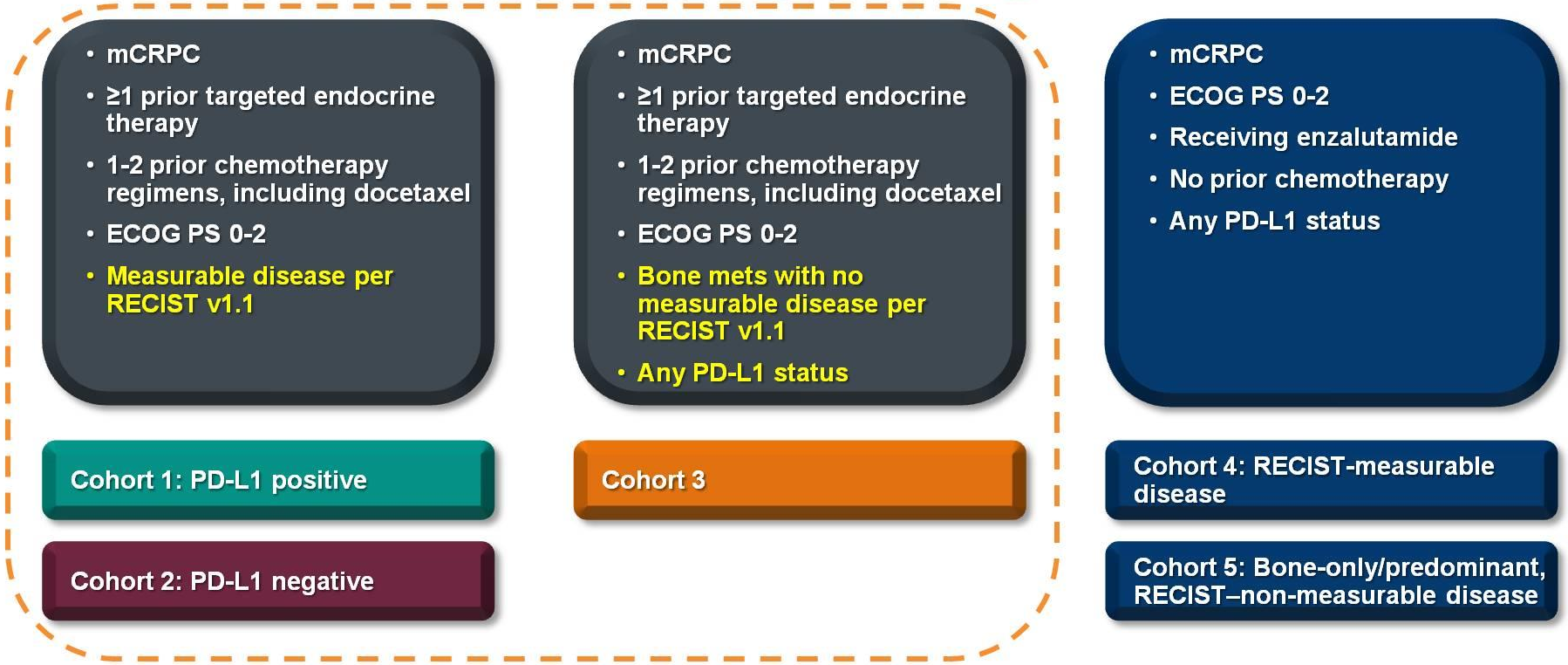


# Enzalutamide and Apalutamide for M0 CRPC

- Both studies used PSADT $\leq$ 10 months
- Metastasis-free survival as endpoint
  - Overall survival data not yet mature
- Do current advances in imaging modalities (e.g PSMA PET) make M0 CRPC an extinct diagnosis?

# Immunotherapy: Checkpoint inhibition

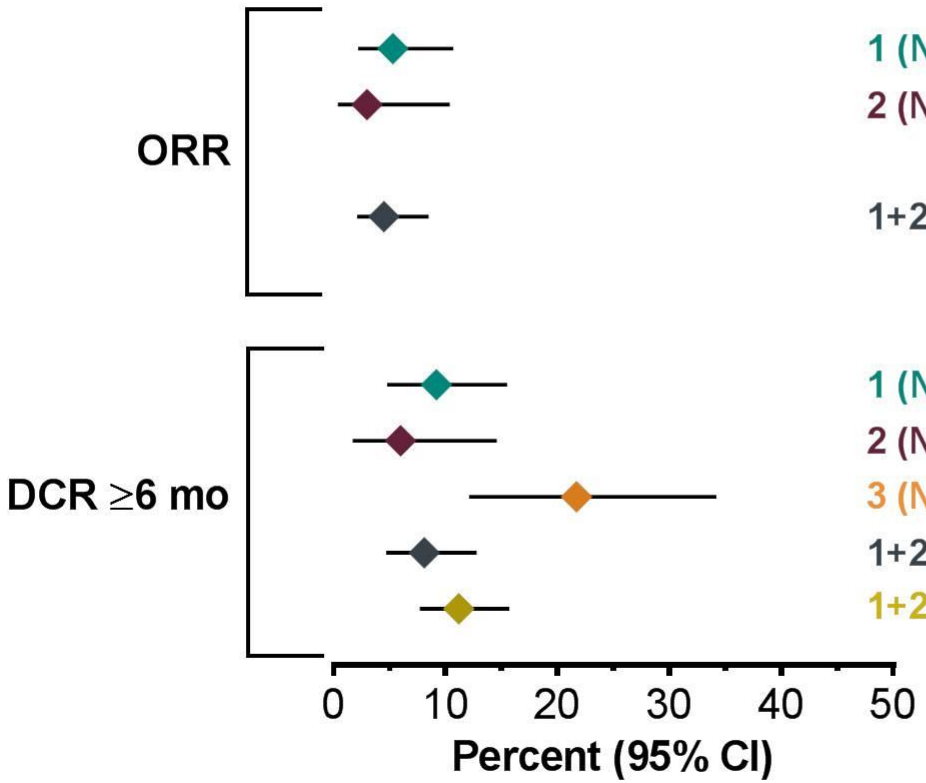
## KEYNOTE-199 Study Design




**Treatment in all cohorts:** pembrolizumab 200 mg Q3W for 35 cycles or until confirmed PD, intolerable toxicity, investigator decision, or patient withdrawal

ClinicalTrials.gov, NCT02787005.

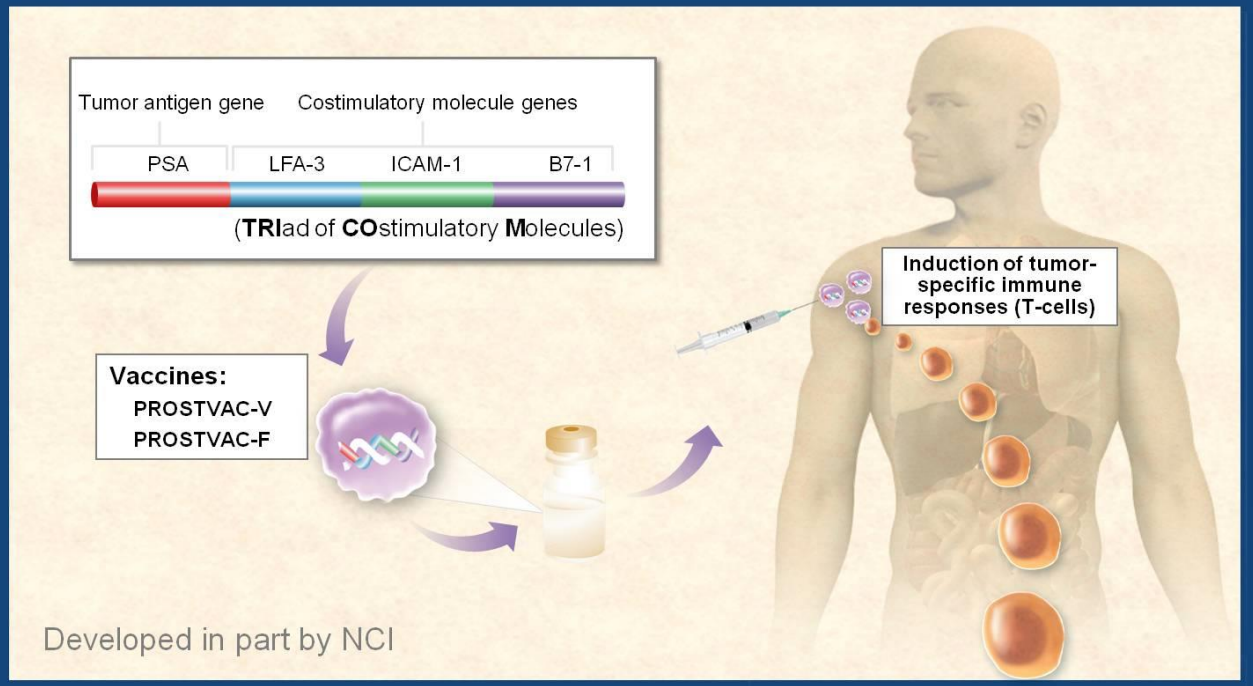
# Response Rate and Disease Control Rate
## RECIST v1.1, Central Review




| Cohort | Rate, n (%) | DOR, median (range) |
|---|---|---|
| 1 (N = 131) | 7 (5%) | 8.4 mo (1.9 to 10.6+) |
| 2 (N = 67) | 2 (3%) | NR (4.4 to 7.2+ mo) |
| 1+2 (N = 198) | 9 (5%) | 8.4 mo (1.9 to 10.6+) |
| 1 (N = 131) | 12 (9%) | |
| 2 (N = 67) | 4 (6%) | |
| 3 (N = 60) | 13 (22%) | |
| 1+2 (N = 198) | 16 (8%) | |
| 1+2+3 (N = 258) | 29 (11%) | |

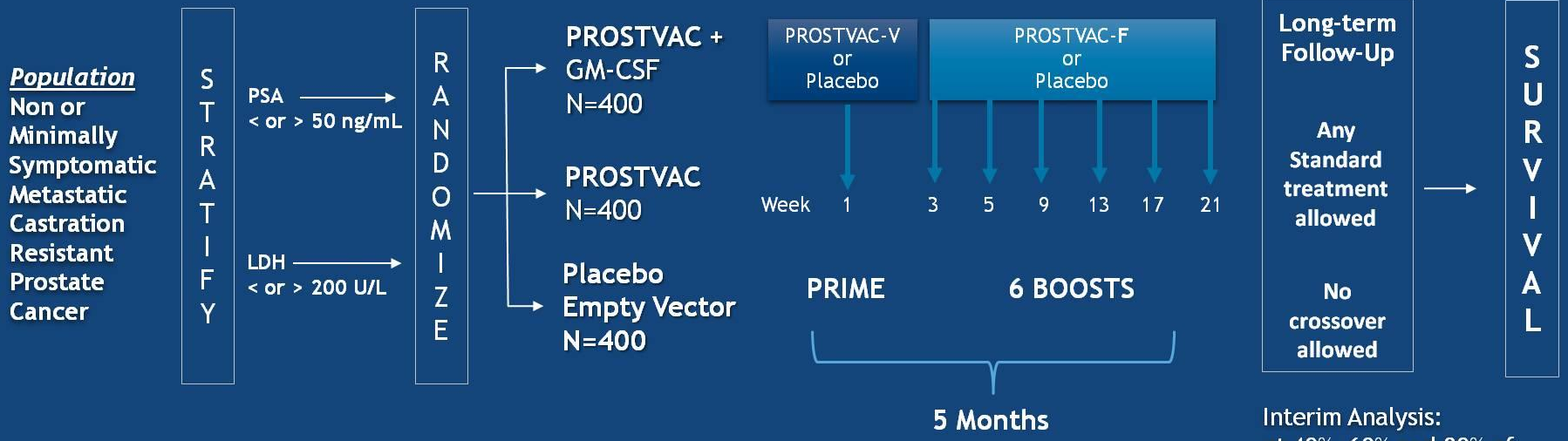
DCR ≥6 mo includes patients with best response of CR or PR of any duration or SD or nonCR/nonPD of ≥6 mo duration. Data cutoff date: Oct 13, 2017.

# Immunotherapy: Therapeutic Cancer Vaccine approach




NIH Medical Arts and Photography

# PROSPECT Phase 3 Design

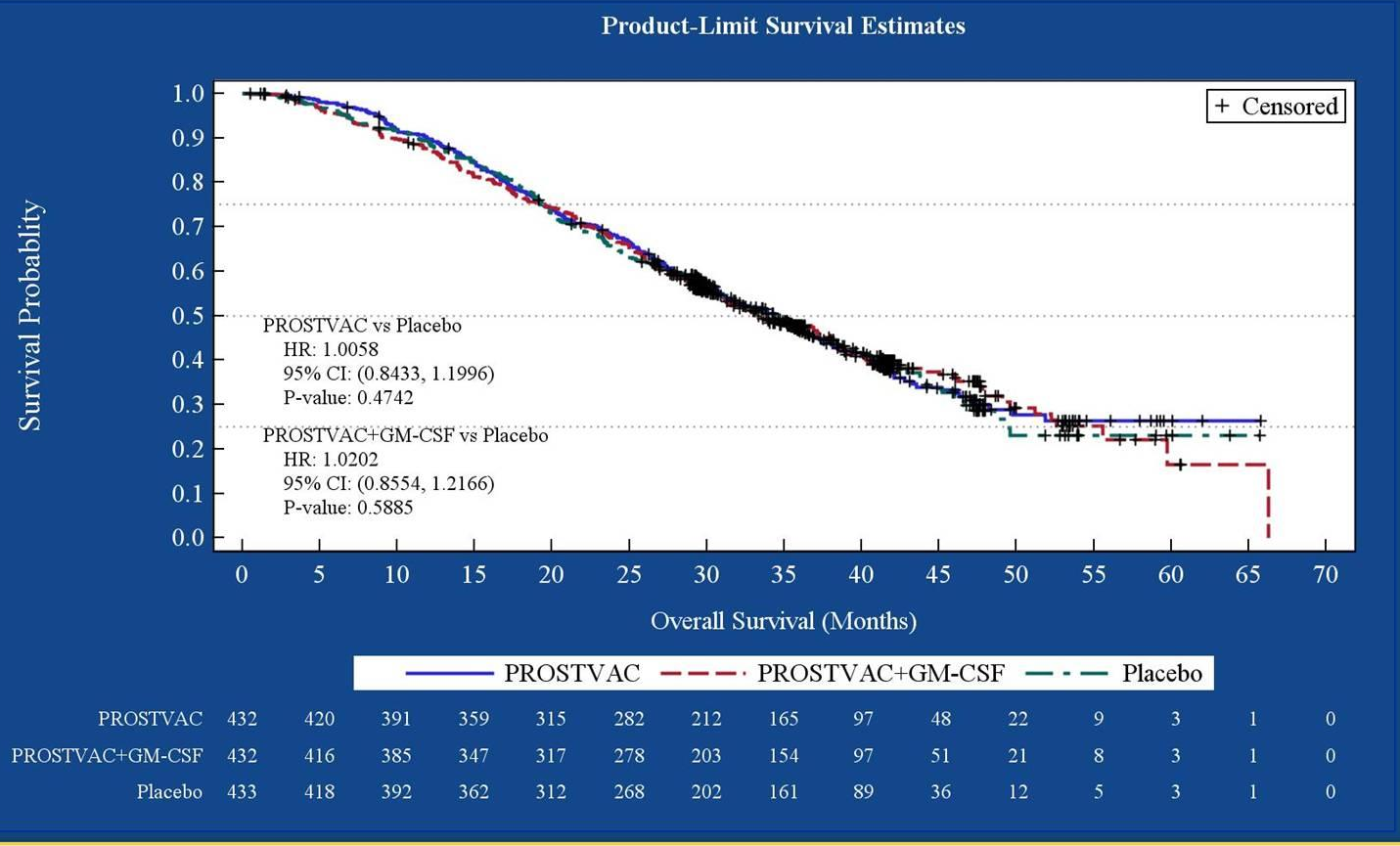



- **Primary Endpoint:** **Overall Survival**
- Secondary Endpoint: Event-Free Survival at 6 Months

Interim Analysis:
at 40%, 60% and 80% of the expected events

Two comparisons:
PROSTVAC vs Pbo
PROS + GM vs Pbo

# Overall Survival ITT




| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PROSTVAC | 432 | 420 | 391 | 359 | 315 | 282 | 212 | 165 | 97 | 48 | 22 | 9 | 3 | 1 | 0 |
| PROSTVAC+GM-CSF | 432 | 416 | 385 | 347 | 317 | 278 | 203 | 154 | 97 | 51 | 21 | 8 | 3 | 1 | 0 |
| Placebo | 433 | 418 | 392 | 362 | 312 | 268 | 202 | 161 | 89 | 36 | 12 | 5 | 3 | 1 | 0 |

Sep 2017
Interim Analysis #3
DMC recommended closure of the study on grounds of futility

| Median OS | |
|---|---|
| PROSTVAC | 34.4 |
| PROSTVAC+ GM-CSF | 33.2 |
| Placebo | 34.3 |

# Immunotherapy in CRPC

- Still not a robust role for single-agent immune checkpoint inhibition in mCRPC
- PROSTVAC as a single agent is not beneficial in mCRPC
- Combination approaches may be necessary to realize potential of immunotherapy in CRPC

# Combination approaches with PARP inhibitors

## Olaparib + Durvalumab in mCRPC

**Primary Objective:**

- To determine efficacy as measured by progression-free survival (PFS) consistent with 70% PFS at 4 months

**Secondary Objectives:**

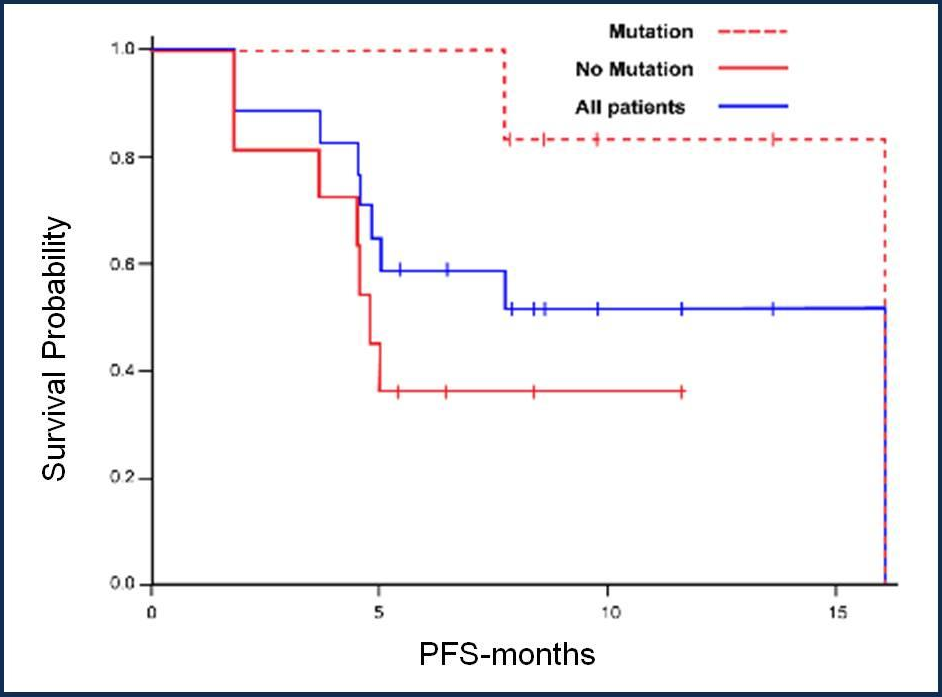
- Safety
- Response rate as measured by PSA and imaging

**Key Exploratory Objectives:**

- Mutational analysis on mandatory on-study biopsies
- Chemokine and cytokine analysis
- Peripheral immune subsets

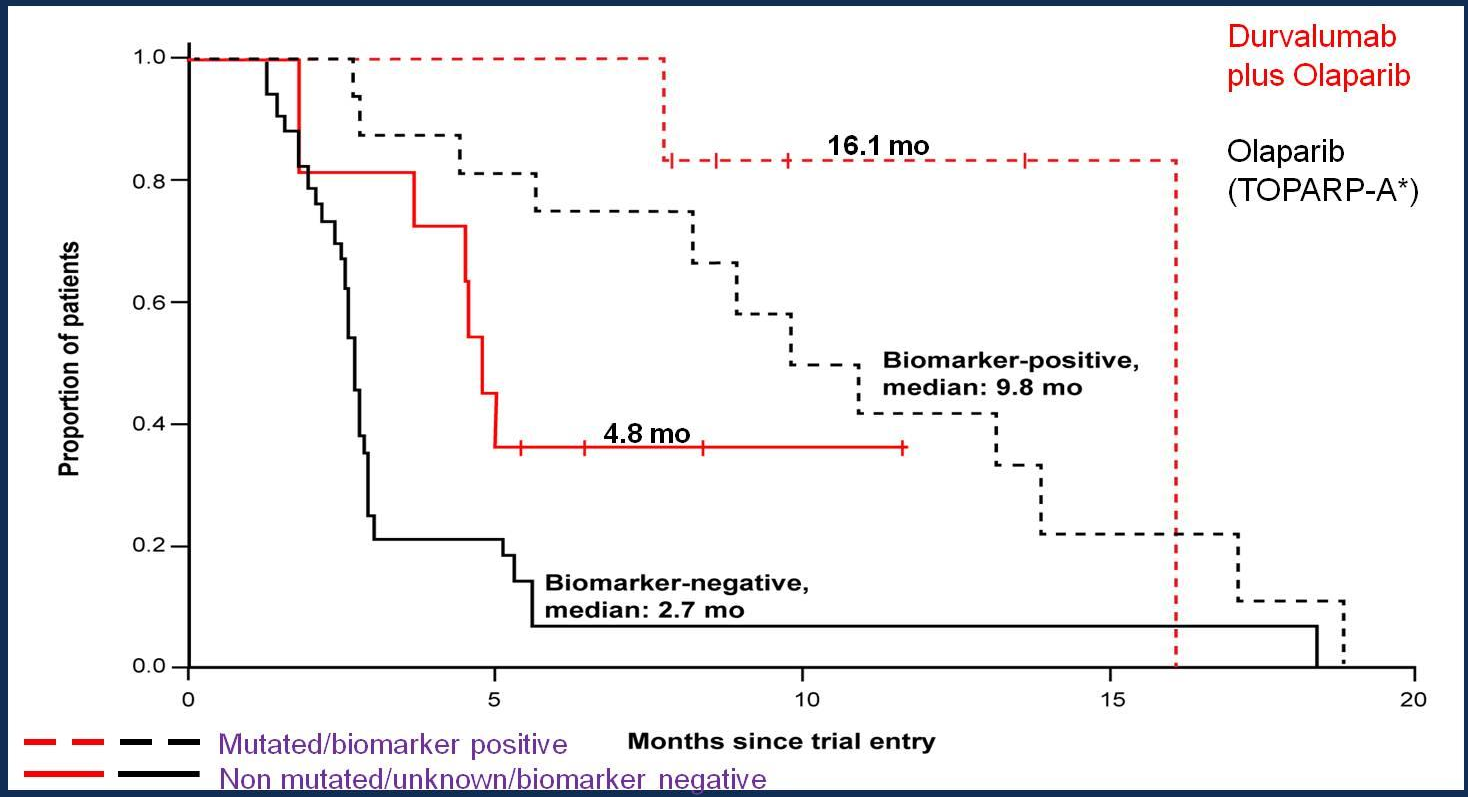

Mandatory on-study biopsy

# Median Radiographic PFS




- All patients: 16.1 months (95% CI: 4.5-16.1 months)
- Non-mutated/unknown: 4.8 months (95% CI: 1.8 months- cannot be calculated)
- Mutated: 16.1 months (95% CI: 7.8-18.1 months)

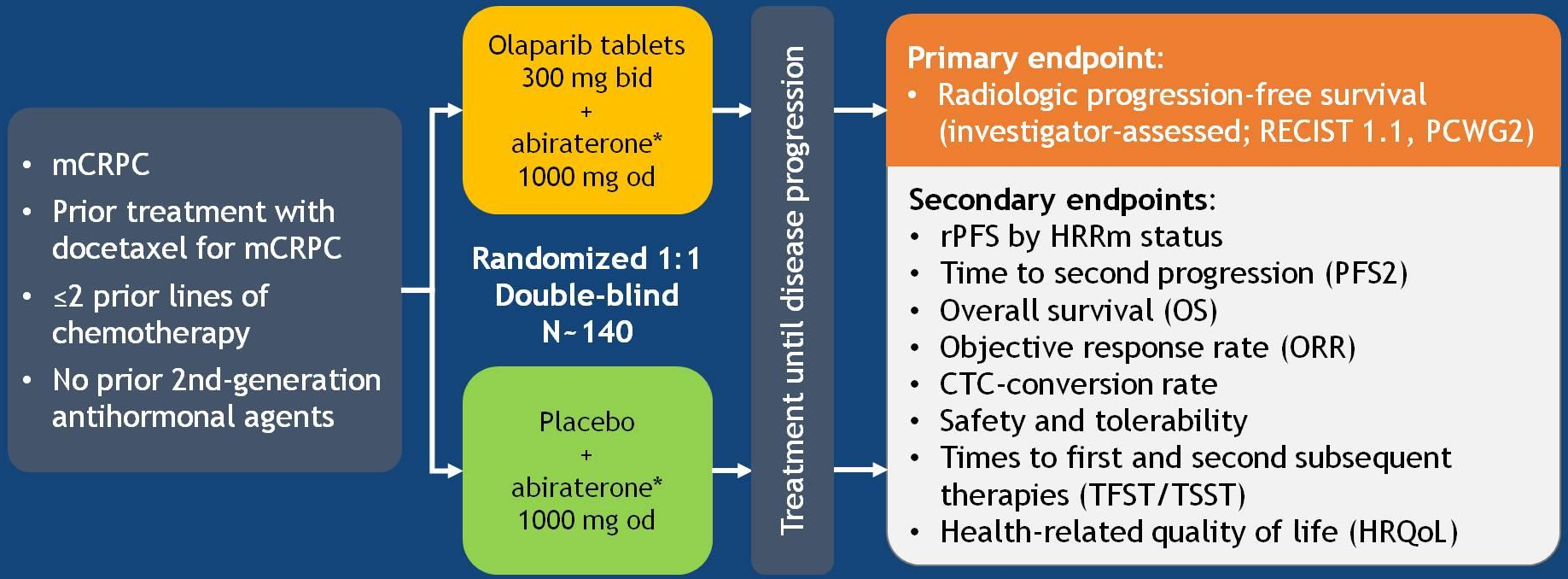
# Radiographic PFS of TOPARP-A and Durvalumab plus Olaparib




*Mateo J et al. N Engl J Med. 2015

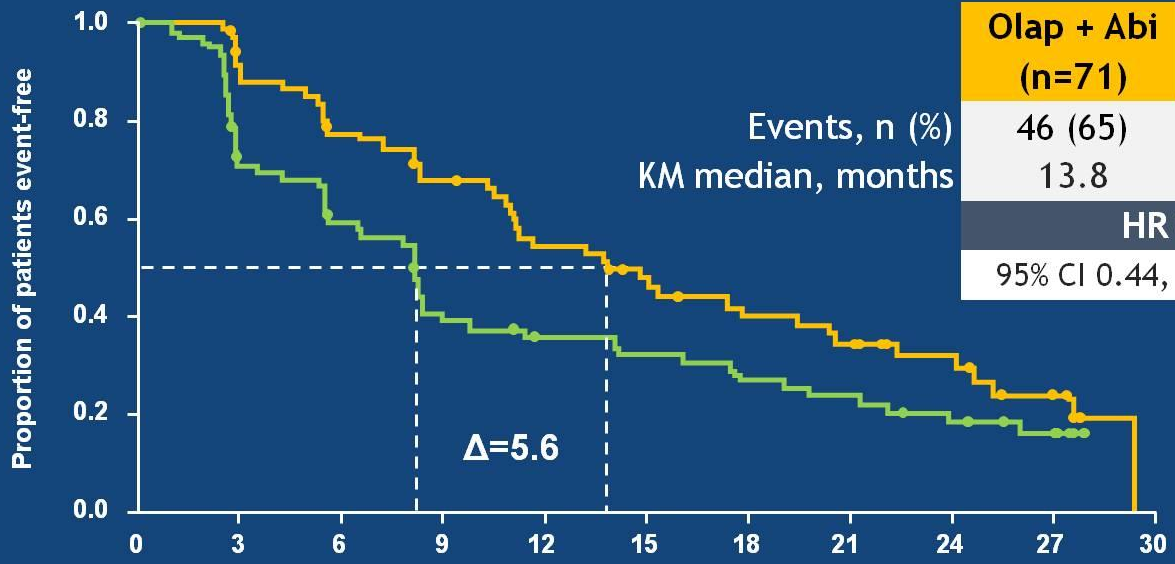
# Combination approaches with PARPi

## Trial design




*Prednisone/prednisolone (5 mg) was administered alongside abiraterone as indicated. bid, twice daily; CTC, circulating tumor cell; HRRm, homologous recombination repair gene mutation; mCRPC, metastatic castration-resistant prostate cancer; od, once daily; PCWG, Prostate Cancer Working Group; RECIST, Response Evaluation Criteria in Solid Tumors; rPFS, radiographic progression-free survival

# Primary endpoint: investigator-assessed rPFS




| | Olap + Abi (n=71) | Abi (n=71) |
|---|---|---|
| Events, n (%) | 46 (65) | 54 (76) |
| KM median, months | 13.8 | 8.2 |
| HR 0.65 | | |
| 95% CI 0.44, 0.97; *P*=0.034 | | |

| N at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Olaparib + abiraterone | 71 | 58 | 50 | 42 | 33 | 26 | 21 | 18 | 13 | 8 | 0 |
| Abiraterone | 71 | 48 | 39 | 25 | 21 | 19 | 16 | 14 | 10 | 7 | 0 |

Abi, abiraterone; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; olap, olaparib

# rPFS by HRR mutation status

## HRRm

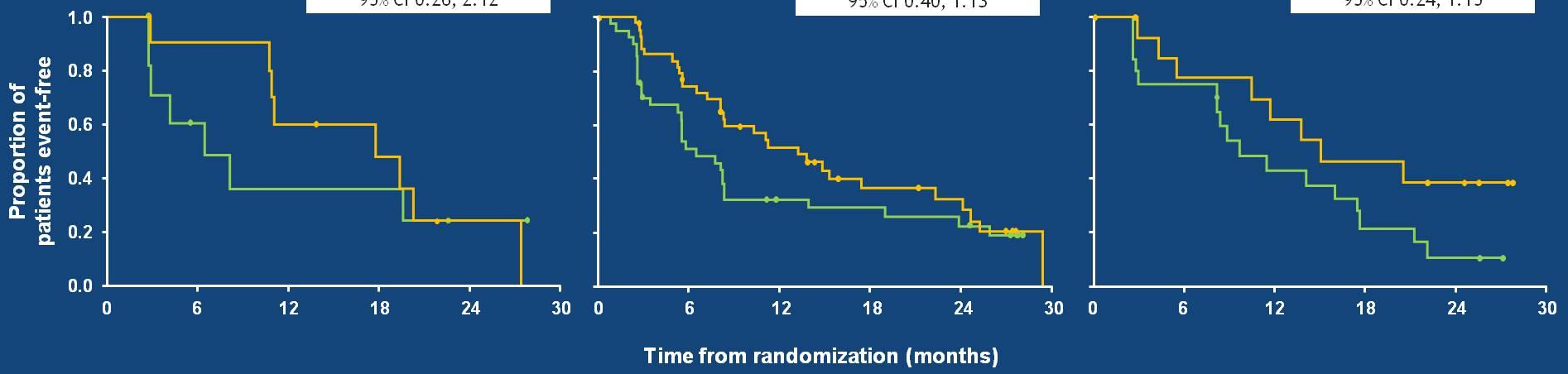
| | Olap + Abi (n=11) | Abi (n=10) |
|---|---|---|
| Events, n (%) | 8 (73) | 7 (70) |
| KM median, months | 17.8 | 6.5 |
| HR 0.74 | | |
| 95% CI 0.26, 2.12 | | |

## HRRpc*

| | Olap + Abi (n=45) | Abi (n=41) |
|---|---|---|
| Events, n (%) | 30 (67) | 30 (73) |
| KM median, months | 13.1 | 6.4 |
| HR 0.67 | | |
| 95% CI 0.40, 1.13 | | |

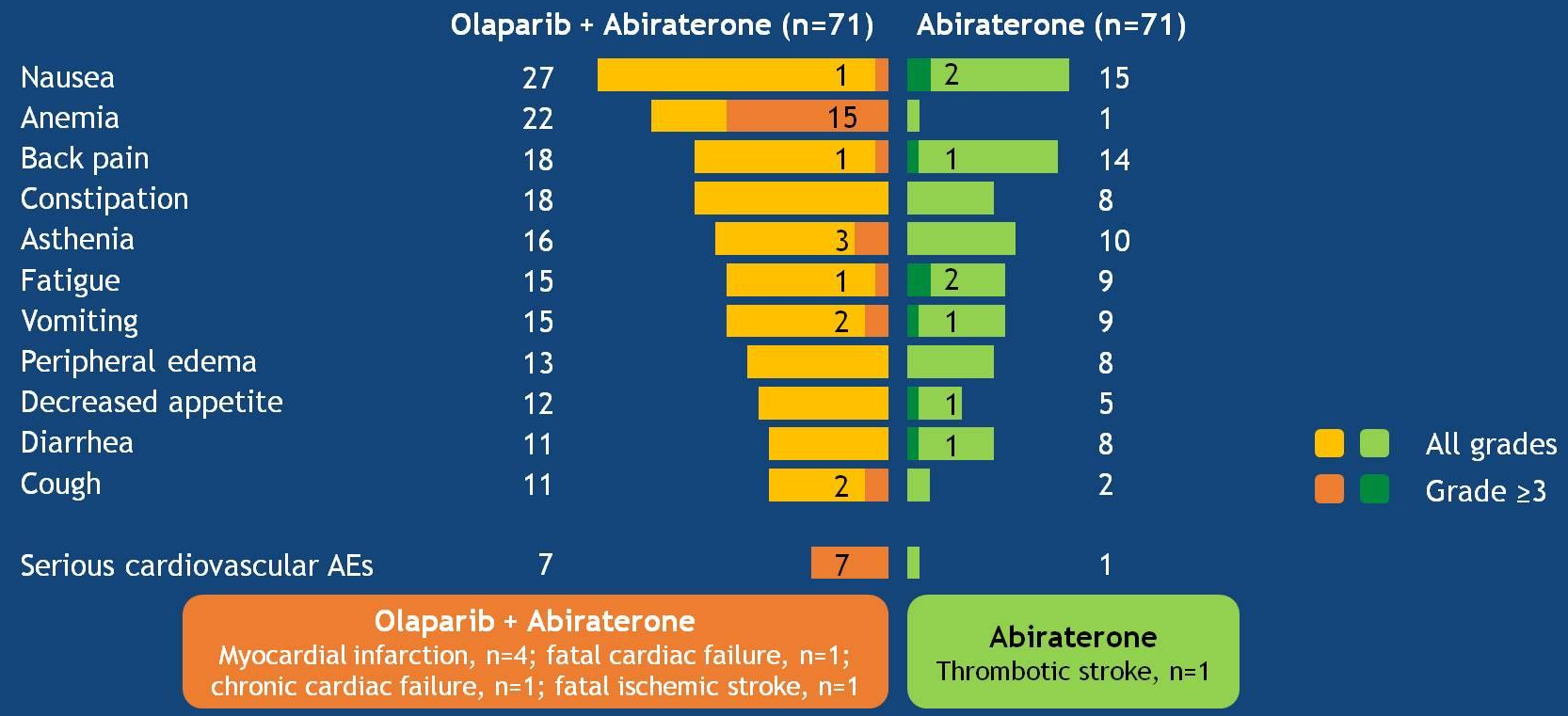
## HRRwt

| | Olap + Abi (n=15) | Abi (n=20) |
|---|---|---|
| Events, n (%) | 8 (53) | 17 (85) |
| KM median, months | 15.0 | 9.7 |
| HR 0.52 | | |
| 95% CI 0.24, 1.15 | | |




*80/86 patients HRRwt by plasma and/or germline testing
HRRpc, HRR partially characterized; HRRwt, HRR wild-type

# Adverse events experienced by >10 combination arm patients




Numbers inside bars indicate grade ≥3 adverse events

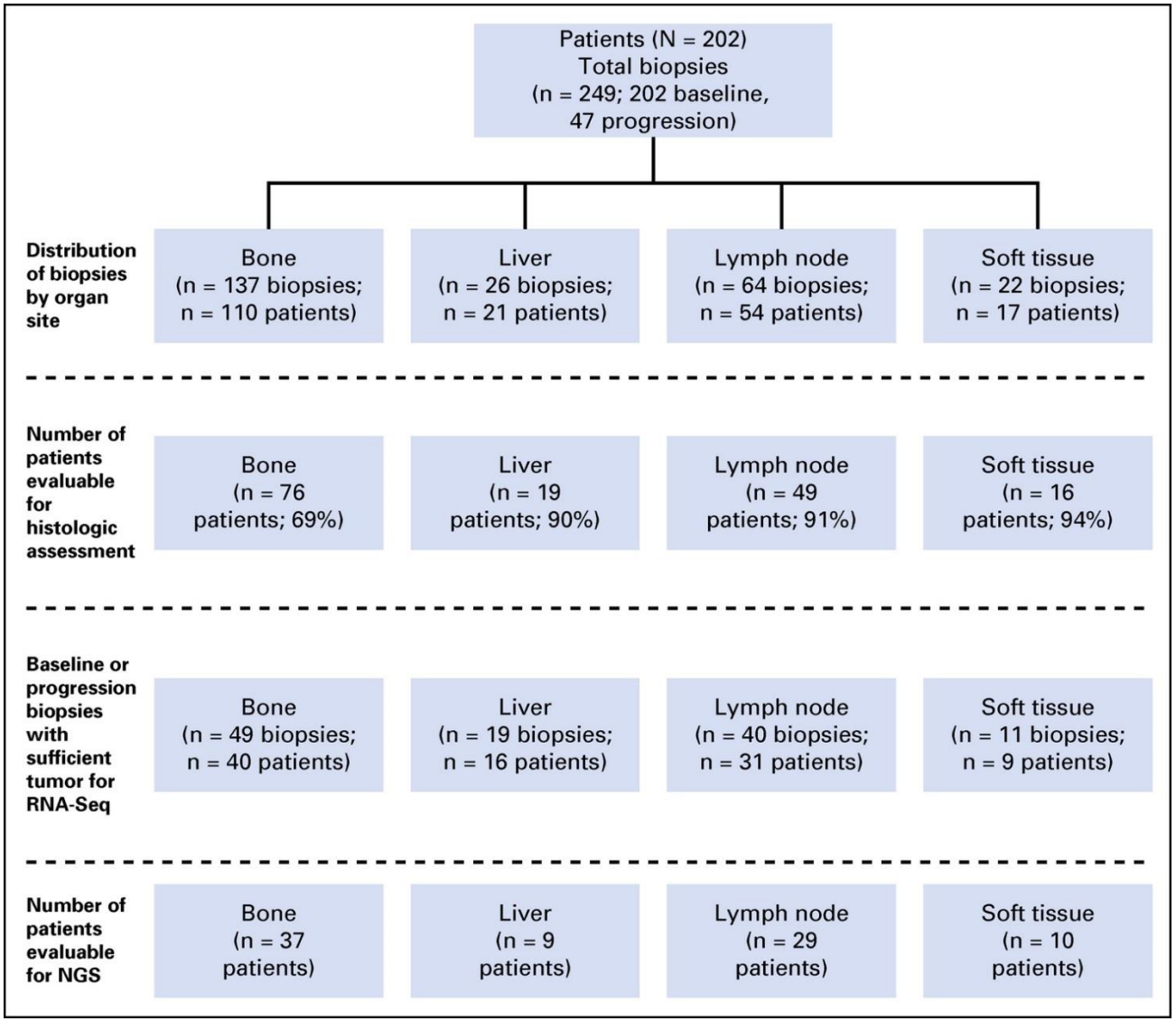
# Role of PARPi in mCRPC

- Activity of PARPi plus immune checkpoint inhibitor (olaparib plus durvalumab)
  - But single-arm trial
  - Patients with DNA repair mutations had increased benefit

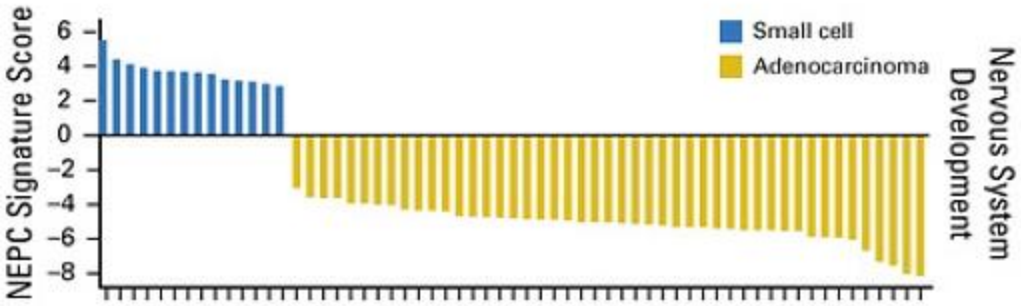
- Activity of PARPi plus abiraterone + prednisone
  - Subset analysis shows those with wt HRR status did better
  - CV safety signal of the combination

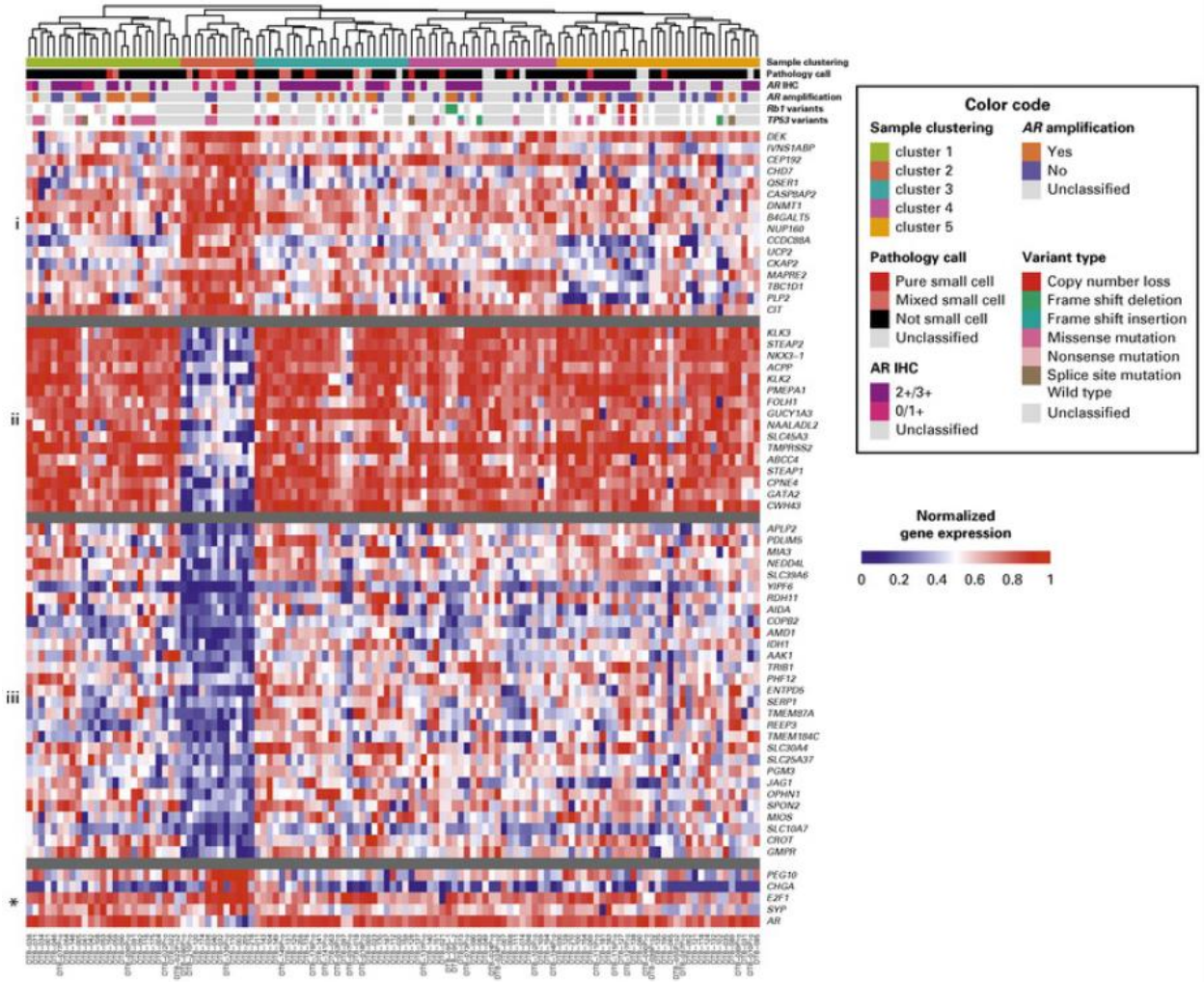
# Identifying Evolution of mCRPC

- Prospective trial of patients with progressive mCRPC
- Biopsies required (at least one bone or soft tissue)
- Follow-up biopsies optional
- Followed prospectively for OS




Aggarwal et al J Clin Oncol 2018



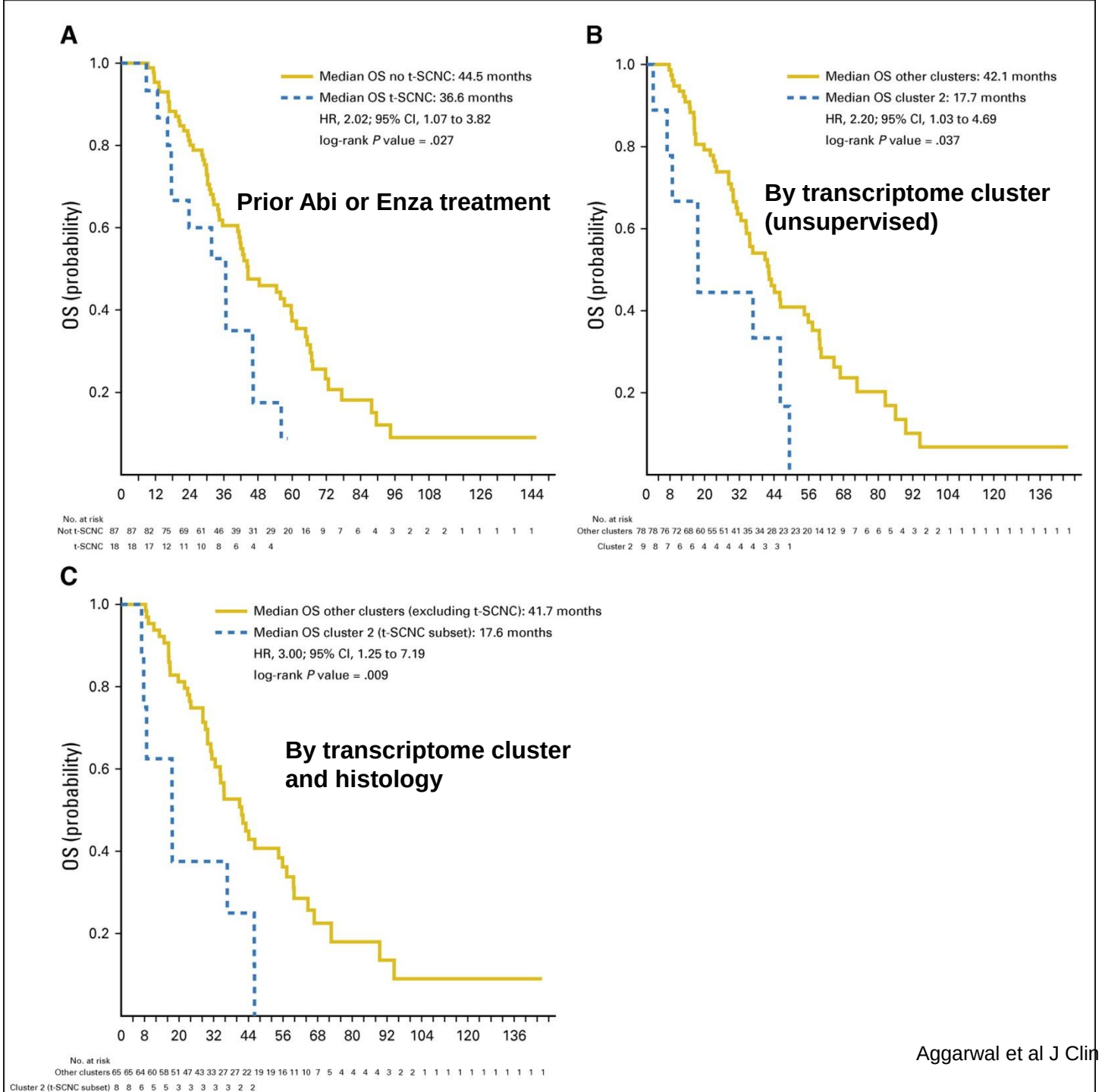




# Findings

t-SCNC incidence: 17%

Distinct transcriptome signature

Aggarwal et al J Clin Oncol 2018

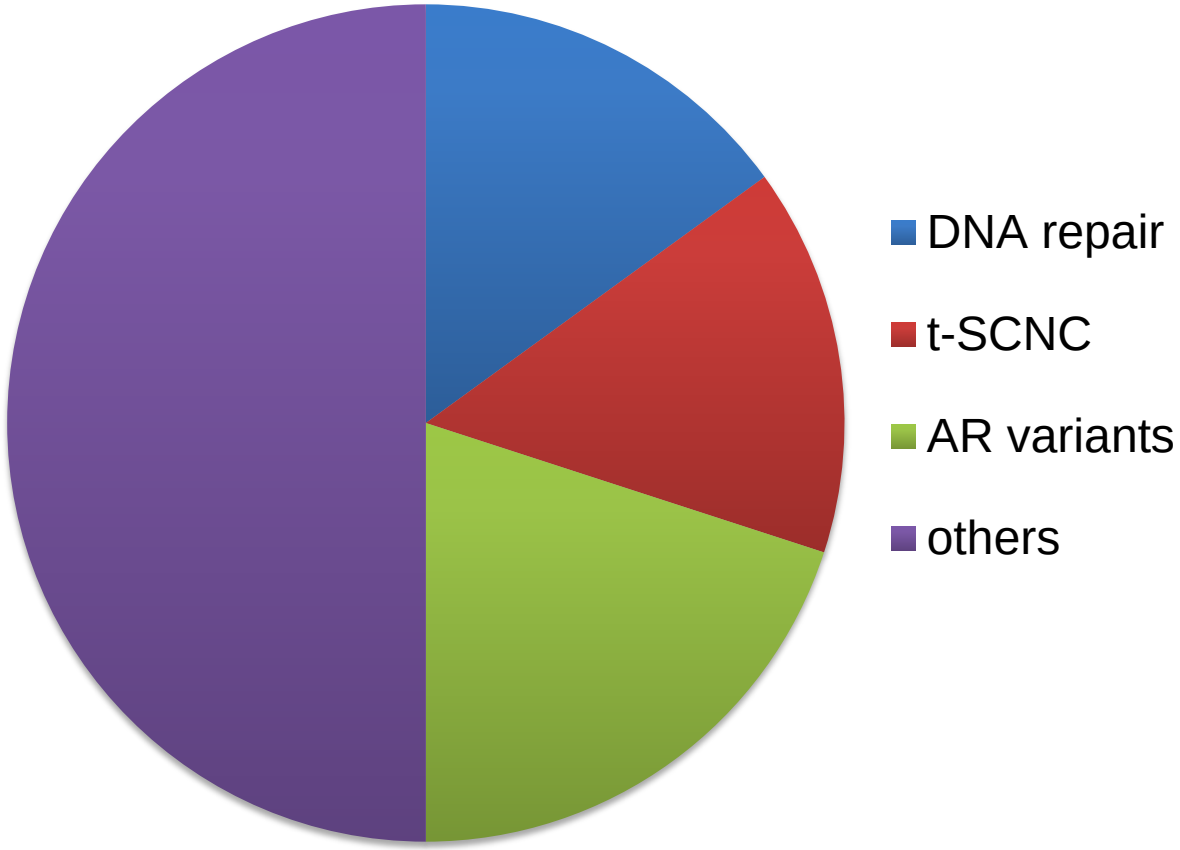



Aggarwal et al J Clin Oncol 2018

# Genomic characterization of mCRPC subtypes

- t-SCNC has distinct transcriptome signature
  - AR amplification (67%) & protein expression (75%) present
  - nearly mutually exclusive with DNA repair mutations
- Outcomes are worse for these patients (HR 2)
- Indicates a need for trials aimed at this population

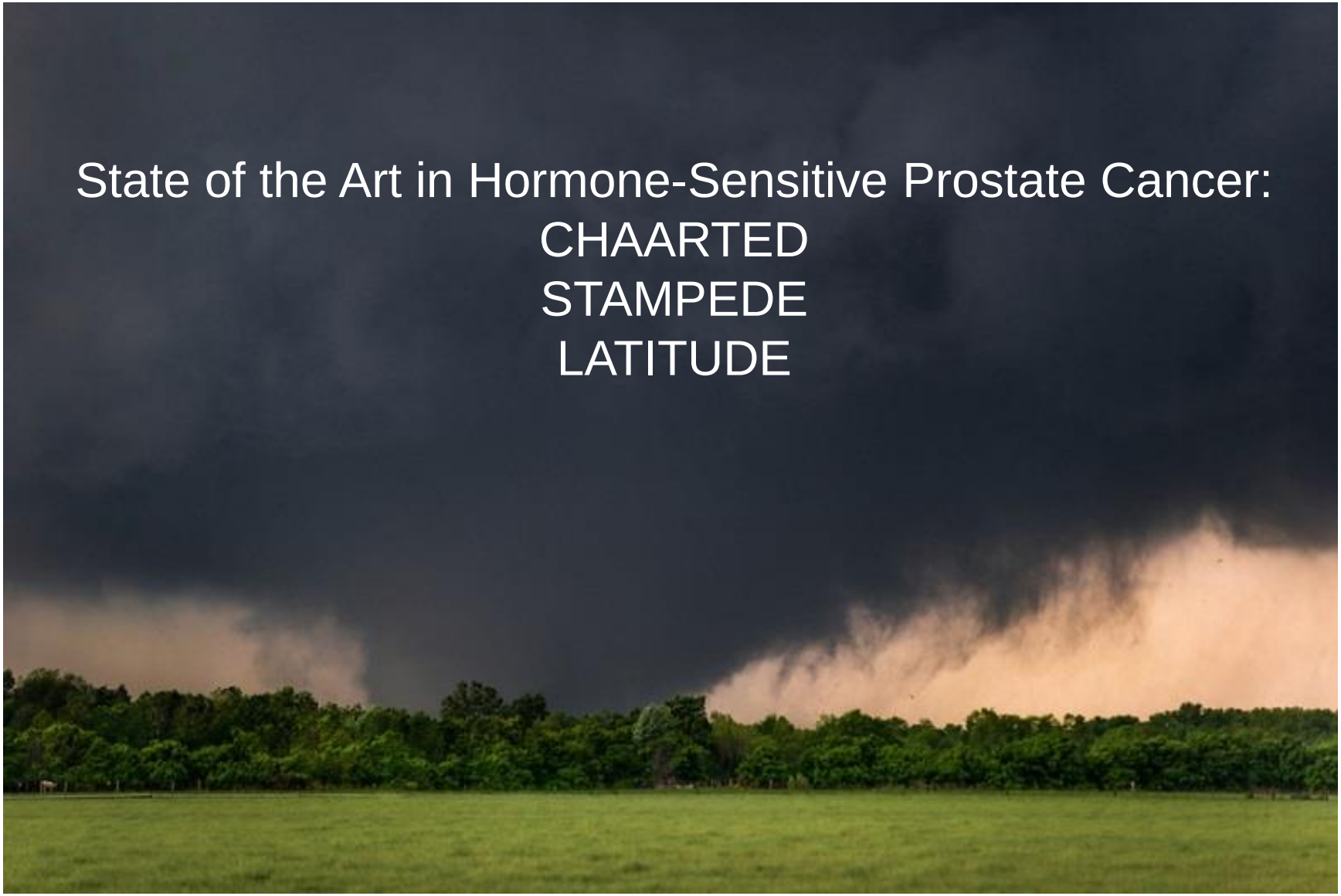
# Becoming more precise with prostate cancer



# State of the Art 2018

- M0 CRPC
  - Apalutamide and enzalutamide
    - Albeit, may be a disappearing disease
- Immunotherapy
  - Combination approach likely needed
- DNA repair pathway
  - Combination approaches require further study
- t-SCNC
  - Distinct gene signature → better therapies

# The future of CRPC in context

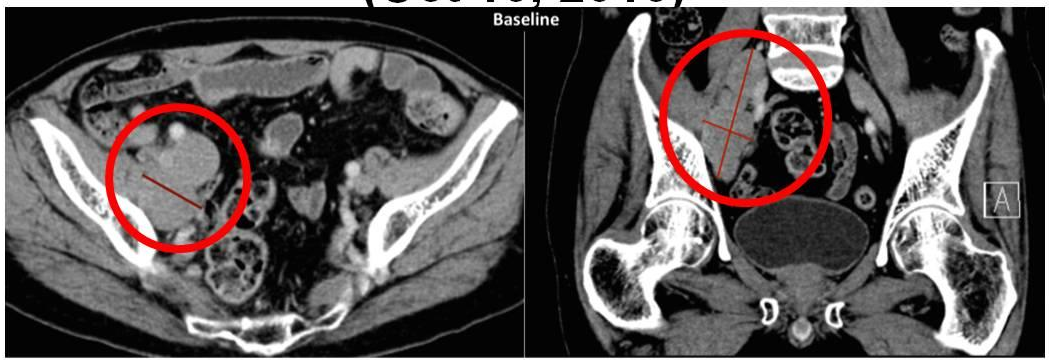


# Appendix

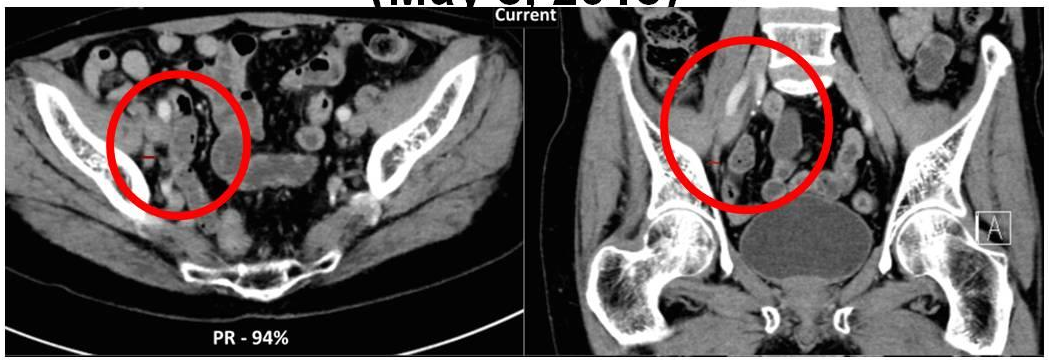
# Responder 1

- Disease course
  - Initial diagnosis: TXNXM0 GS9 (4 + 5) high-risk disease (Jul 2010)
  - Metastasized to lymph nodes (Sep 2014)
- Prior systemic therapy
  - Bicalutamide (Oct 2011-Sep 2014)
  - Docetaxel (Apr 2015-Oct 2015)
  - Enzalutamide (Oct 2015-Mar 2016)
- Enrolled in KEYNOTE-199 cohort 1
  - Age 67 years
  - First pembro dose: Nov 8, 2016
  - Cycle 24 of pembro: May 9, 2018
  - **RECIST: 94% reduction**

**Baseline (Oct 16, 2016)**




**Current (May 8, 2018)**




***Patient was treated at the Royal Marsden in London, UK. Images courtesy of Johann de Bono.***

# Genomic Analysis of Responders: Whole Exome Sequencing

- 6 of 9 responders with available data: 5/7 from cohort 1 (PD-L1+), 1/2 from cohort 2 (PD-L1–)
- **4 of 6 with mutations in DDR genes**: 3/5 from cohort 1 (PD-L1+), 1/1 from cohort 2 (PD-L1–)

| Patient 1 (Cohort 1) | Patient 2 (Cohort 1) | Patient 3 (Cohort 2) | Patient 4 (Cohort 1) |
|---|---|---|---|
| *ATM* splice site acceptor deletion | *TP53* R273P substitution | *BRCA2* V1176Gfs*8 insertion | *NBN* Q494P substitution |
| *BRCA2* A1162V substitution | | | *TP53* S241F substitution |
| *CDK12* G1461Afs* deletion | | | |
| *FANCA* substitution | | | |
| *FANCD2* R263H substitution | | | |
| *MLH3* T930Qfs*35 deletion | | | |
| *RAD54L* R511H substitution | | | |

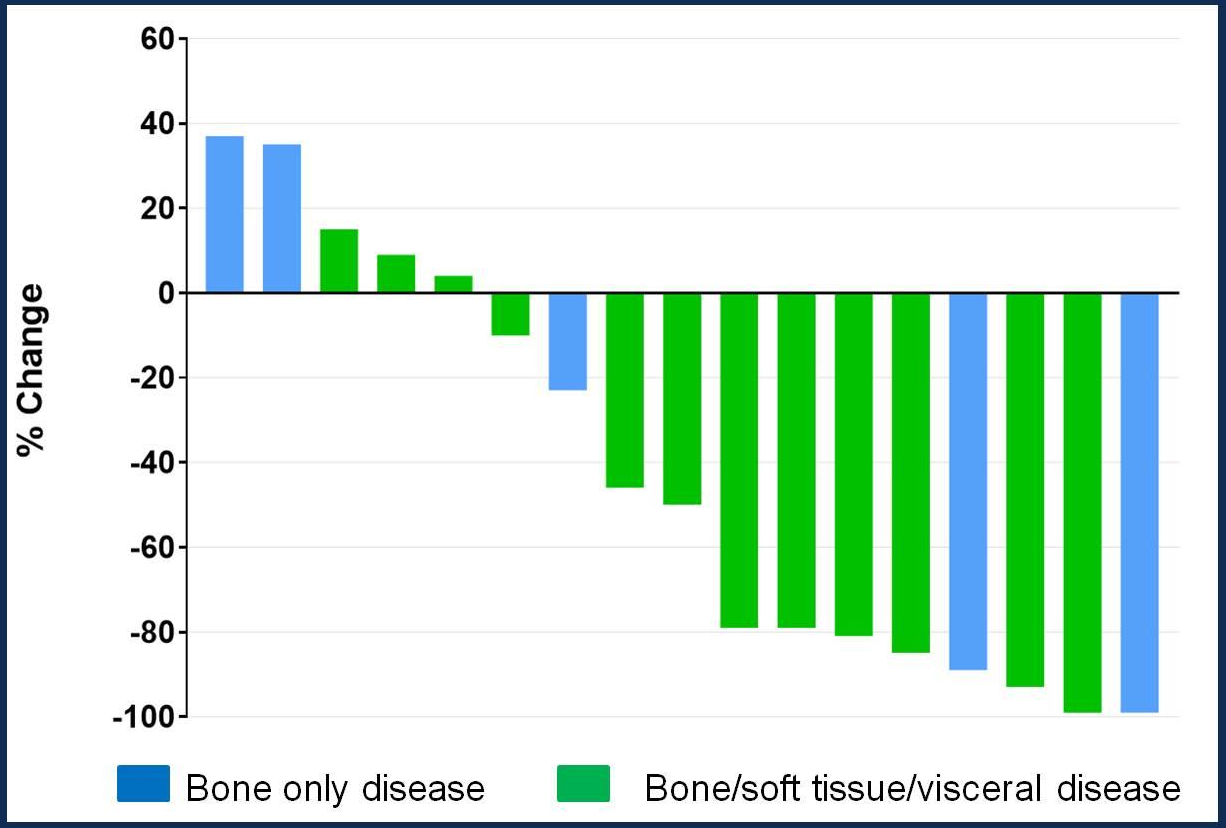
DNA damage repair (DDR) genes examined: *ATM*, *ATR*, *BAP1*, *BARD1*, *BLM*, *BRAP*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK12*, *CENPQ*, *CHEK1*, *CHEK2*, *EPCAM1*, *ERCC1*, *ERCC2*, *ERCC3*, *ERCC4*, *ERCC6*, *FAM175A*, *FAM175B*, *FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*, *FANCI*, *FANCL*, *GEN1*, *HDAC2*, *MLH1*, *MLH3*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIF1*, *PMS2*, *RAD51*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*, *RDM1*, *TP53*, and *XRCC2*.
Data cutoff date: Oct 13, 2017.

# Protocol Mandated On-Study Biopsy Results

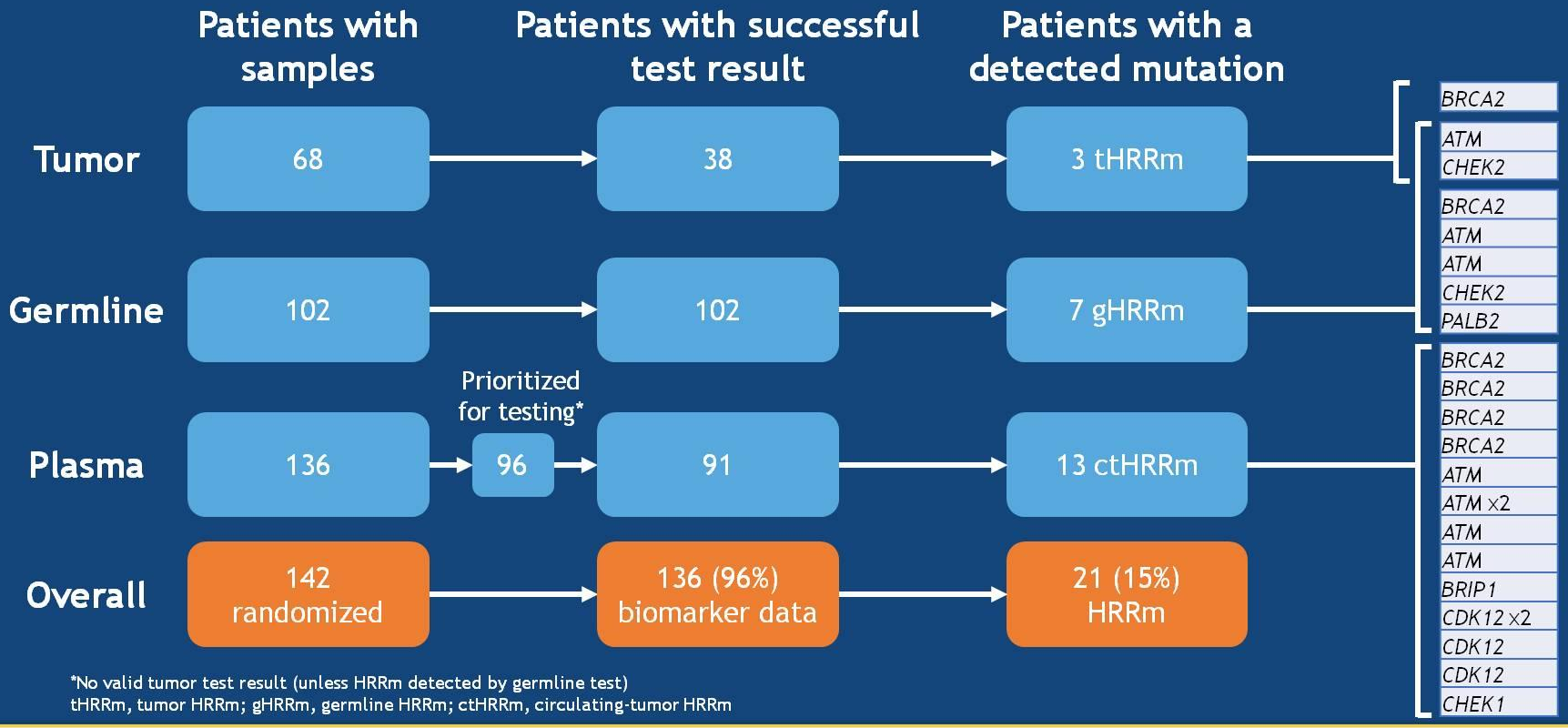
| Patient Number | DNA Damage Repair (DDR) Pathway Mutation(s) | Other Genomic Aberration(s) | Maximum % PSA Decline |
|---|---|---|---|
| 1 | BRCA2 | None | -79% |
| 2 | BRCA2 | ASXL1 | -99% |
| 3 | None | TP53, RB1 | 15% |
| 4 | None | AR amplification | 35% |
| 5 | None | MYD88, CCND3, BIRC3 | -79% |
| 6 | BRCA2 (germline) | SPOP, 13q deletion, AR amplification | -89% |
| 7 | Insufficient specimen | Insufficient specimen | -99% |
| 8 | BRCA2 (germline) | 13q deletion, PKP2 | -93% |
| 9 | Insufficient specimen | Insufficient specimen | -23% |
| 10 | BRCA2 | TP53, KAT6A | -85% |
| 11 | BRCA2 (germline) | Copy number loss and allelic imbalance on 13q | -50% |
| 12 | None | RYR2, PIK3CA | 37% |
| 13 | Insufficient specimen | Insufficient specimen | 9% |
| 14 | BRCA2 | HRAS | -80% |
| 15 | None | PIK3CA, ADGRB3, TP53 | 4% |
| 16 | None | TP53, STAG1 | -46% |
| 17 | None | BRAF, AR amplification, ASXL1, MYH11 | -10% |

- OncoVar DNA sequencing analysis of 500+ genes done by Dr. Paul Meltzer's Lab (Genetics Branch, NCI)
- All mutations are somatic unless otherwise noted

# Maximum Decline in PSA (n=17)



# HRR mutation testing




*No valid tumor test result (unless HRRm detected by germline test)
tHRRm, tumor HRRm; gHRRm, germline HRRm; ctHRRm, circulating-tumor HRRm

# Biomarkers of resistance

## The PROPHECY Trial:

### Multicenter Validation Study of AR-V7 as a Predictive Biomarker in the Context of the Molecular Landscape of CRPC CTCs


- **CTC AR-V7 assays (Epic Nuclear AR-V7, Hopkins AR-V7 Adnatest, Cornell multiplex CTC assay)**
- **Subset CTC and circulating biomarker profiling**:
  CTC WES, CTC CGH, CTC RNASeq, cell free ctDNA, PAXgene MSK multiplex PCR, ctRNA
- **Cellsearch CTC enumeration and validation metastatic biopies**

Prostate Cancer Foundation
Curing Together.

Prospective CiRculating PrOstate Cancer Predictors in HighEr Risk mCRPC StudY

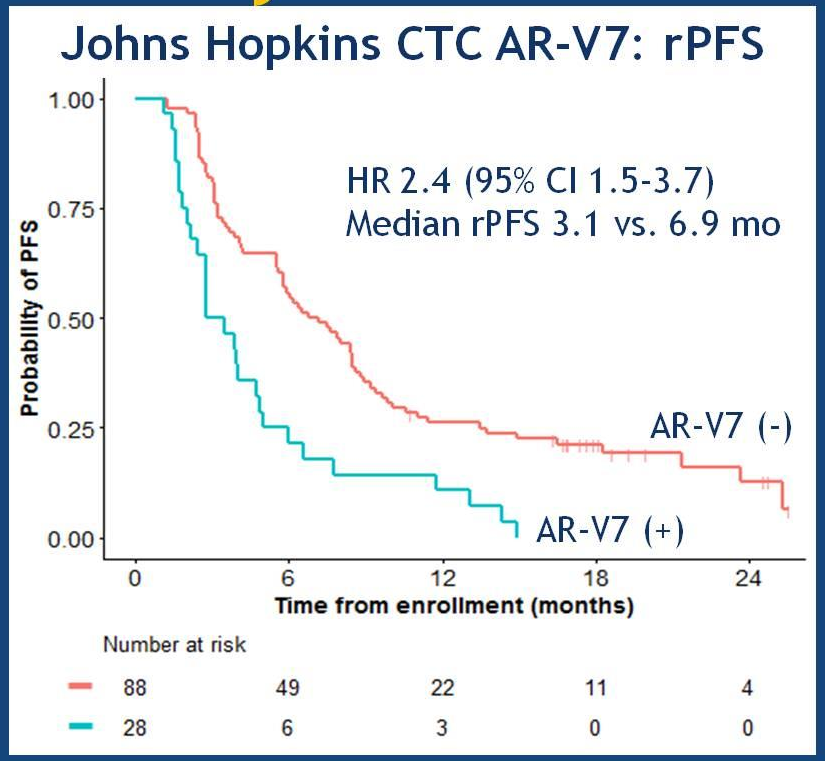
MOVEMBER

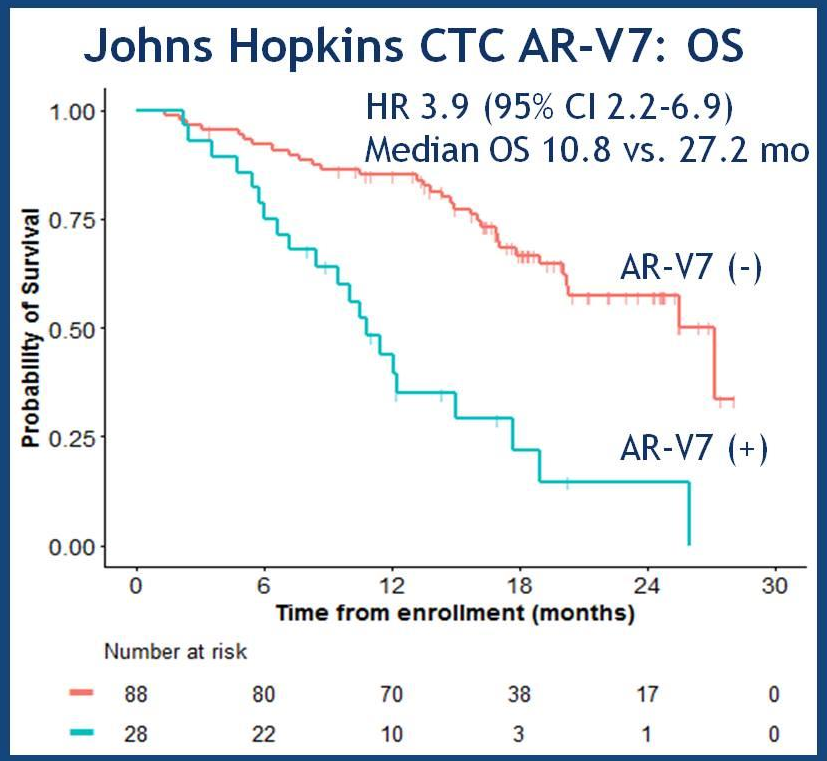
PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: Andrew J Armstrong MD ScM

*US.National Institutes of Health*. 2016
Clinicaltrials.gov/NCT02269982

# Johns Hopkins Modified Adnatest AR-V7 Efficacy Prediction: rPFS and Overall Survival



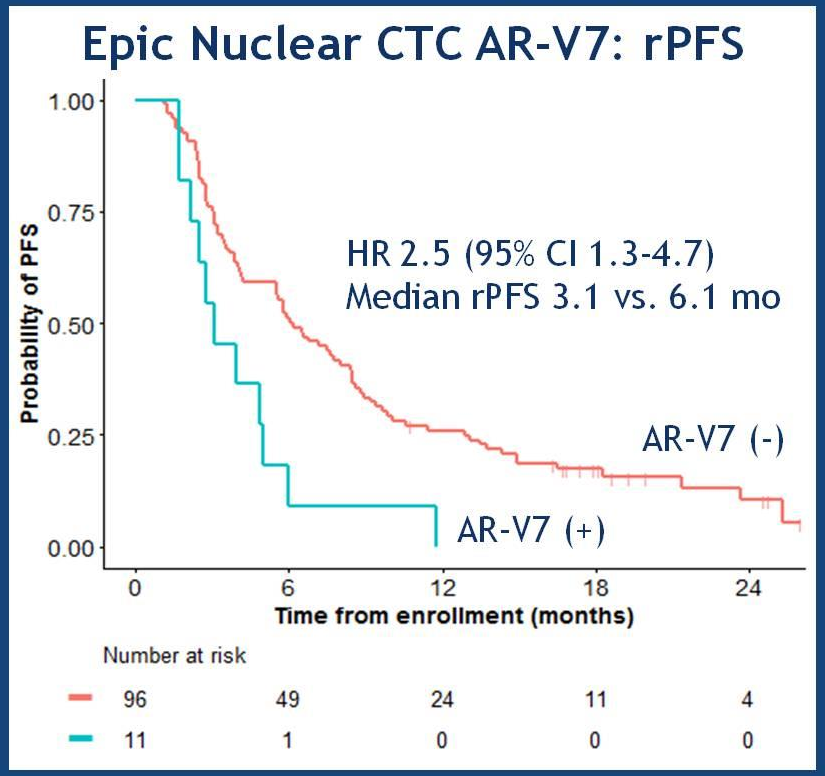



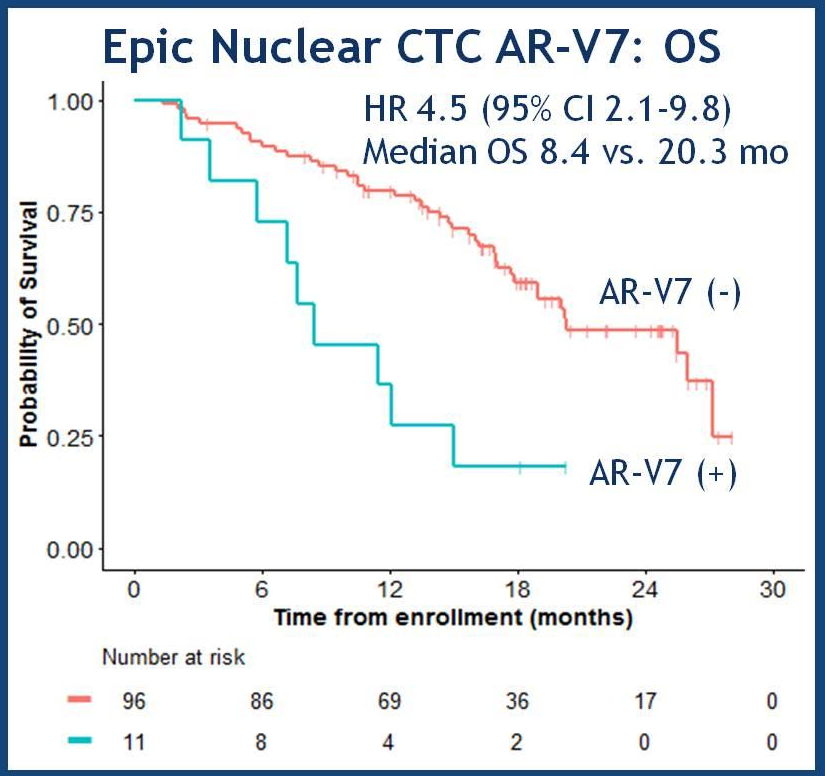





JHU AR-V7 CTC assay met the primary endpoint of the study

# EPIC Nuclear CTC AR-V7 Efficacy Prediction: rPFS and Overall Survival








Epic AR-V7 CTC assay also met the primary endpoint of the study

# Multivariable Analysis: CTC AR-V7 Independently Predicts Short rPFS

| Prognostic Factor | Hazard Ratio (HR) | 95% Confidence Limits (HR) | | p-value |
|---|---|---|---|---|
| AR-V7 + (Adnatest) | 2.19 | 1.30 | 3.69 | 0.0032 |
| Cellsearch CTC, per 7.5 ml | 1.18 | 0.74 | 1.90 | 0.4883 |
| PSA | 1.00 | 0.99 | 1.000 | 0.1039 |
| Alkaline phosphatase | 1.00 | 1.00 | 1.003 | 0.0041 |
| Hemoglobin | 0.96 | 0.84 | 1.10 | 0.5720 |
| Prior enza/abi tx (yes vs. no) | 1.96 | 1.11 | 3.48 | 0.0212 |

| Prognostic Factor | Hazard Ratio (HR) | 95% Confidence Limits (HR) | | p-value |
|---|---|---|---|---|
| AR-V7 + (Epic) | 1.99 | 0.91 | 4.24 | 0.0834 |
| Cellsearch CTCs, per 7.5 mL | 1.39 | 0.87 | 2.22 | 0.1662 |
| PSA | 1.00 | 0.99 | 1.00 | 0.3130 |
| Alkaline phosphatase | 1.00 | 1.000 | 1.000 | 0.0354 |
| Hemoglobin | 0.93 | 0.80 | 1.07 | 0.3056 |
| Prior enza/ AA (yes vs. no) | 1.81 | 1.02 | 3.20 | 0.0427 |

Prediction independent of CTC burden, prior therapy, common validated prognostic factors

# Multivariable Analysis: CTC AR-V7 Independently Predicts Short Overall Survival

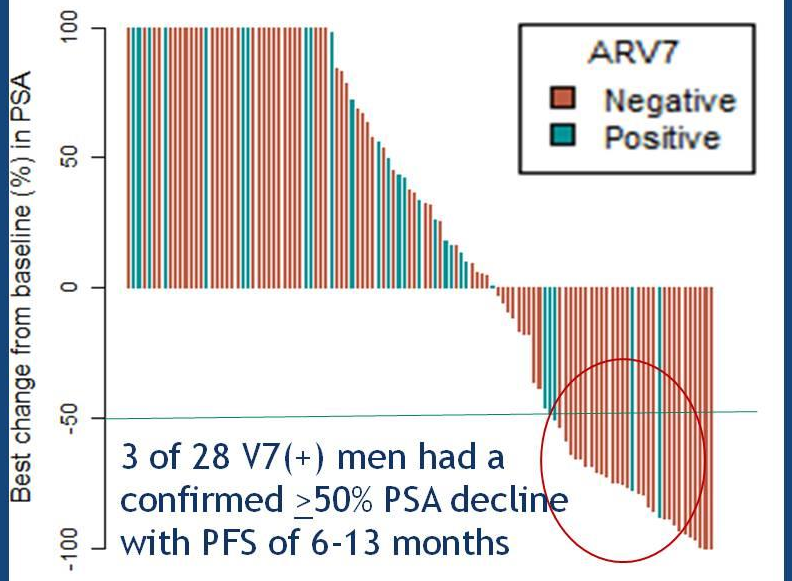
| Prognostic Factor | Hazard Ratio (HR) | 95% Confidence Limits (HR) | | p-value |
|---|---|---|---|---|
| AR-V7 + (Adnatest) | 4.74 | 2.31 | 9.75 | <0.0001 |
| Cellsearch CTC, per 7.5 ml | 0.98 | 0.51 | 1.86 | 0.943 |
| PSA | 1.00 | 0.99 | 1.00 | 0.0153 |
| Alkaline phosphatase | 1.00 | 1.00 | 1.00 | 0.0011 |
| Hemoglobin | 0.77 | 0.64 | 0.93 | 0.0058 |
| Prior enza/abi tx (yes vs. no) | 1.36 | 0.59 | 3.09 | 0.4707 |

| Prognostic Factor | Hazard Ratio (HR) | 95% Confidence Limits (HR) | | p-value |
|---|---|---|---|---|
| AR-V7 + (Epic) | 2.90 | 1.21 | 6.94 | 0.0167 |
| Cellsearch CTCs, per 7.5 mL | 1.37 | 0.73 | 2.59 | 0.3256 |
| PSA | 1.000 | 0.99 | 1.00 | 0.2872 |
| Alkaline phosphatase | 1.00 | 1.000 | 1.00 | 0.0763 |
| Hemoglobin | 0.75 | 0.62 | 0.91 | 0.0036 |
| Prior enza/ AA (yes vs. no) | 1.20 | 0.52 | 2.80 | 0.6726 |

Prediction independent of CTC burden, prior therapy, and common validated prognostic factors

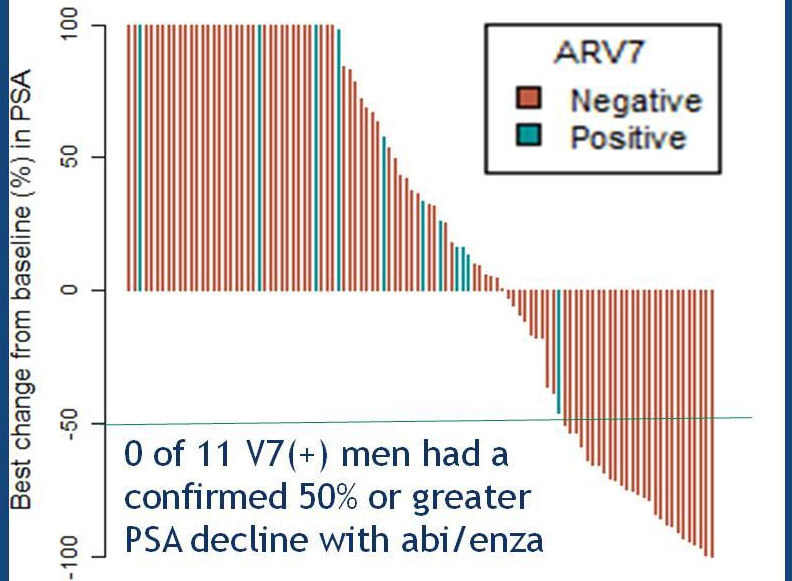
# Confirmed PSA Declines with Abiraterone or Enzalutamide by AR-V7 Status

## Johns Hopkins CTC AR-V7




| Outcome | AR-V7+ / AR-V7- |
|---|---|
| ≥ 50% confirmed PSA decline | 11% / 28% |
| Odds Ratio (95% CI) | 0.31 (0.09-1.12) |

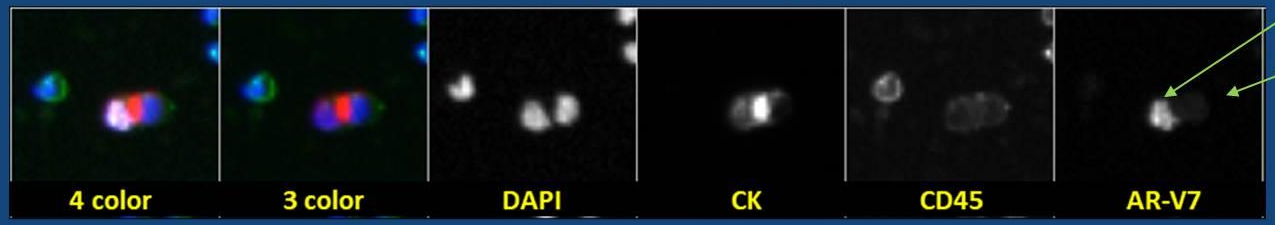
## Epic CTC AR-V7




| Outcome | AR-V7+ / AR-V7- |
|---|---|
| ≥ 50% confirmed PSA decline | 0% / 26% |
| Odds Ratio (95% CI) | Not estimable |

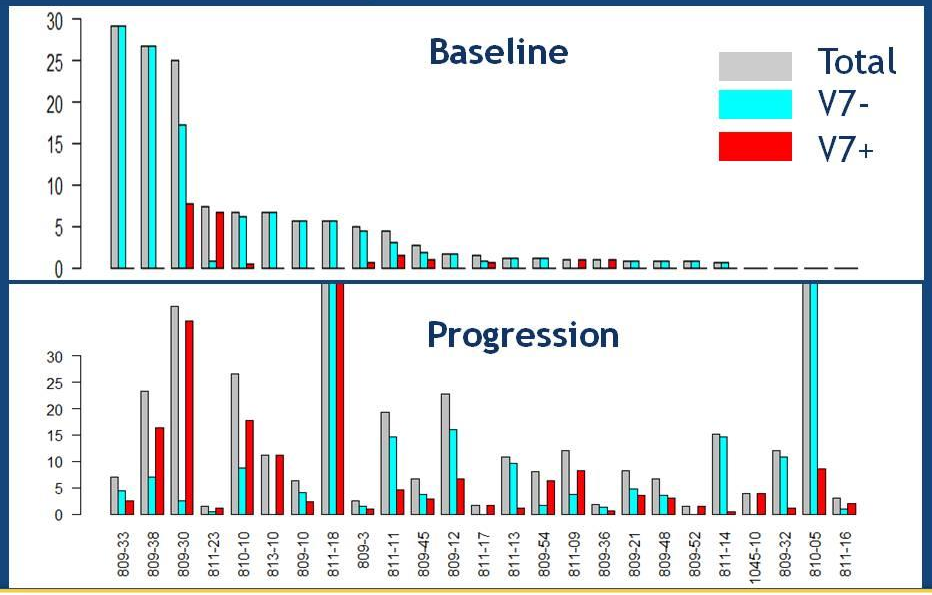
17 JHU AR-V7(+) / Epic AR-V7 (-) patients: PFS 2.8 mo, OS 10.8 mo

# AR-V7 Heterogeneity in CTCs




CTC Cluster with 1 of 2 cells expressing nuclear localized AR-V7

- 63% of AR-V7+ men with mCRPC had high phenotypic heterogeneity (Shannon Index[1]) vs. only 14% of AR-V7 (-) men
- Of AR-V7 (+) men with mCRPC, most CTCs are AR-V7 (-) prior to abi/enza
- However, AR-V7 (+) CTCs can become predominant in some men, especially after progression on enzalutamide/abiraterone








(1) Scher et al Cancer Res 2017

# ARv7 as a biomarker of resistance

- Now have validated biomarker that has decent negative predictive value of response to AR therapies
  - May guide therapy towards chemotherapeutic agents for ARv7 positive patients

- ARv7 negative patients do not always respond to AR therapies
  - More biomarkers needed