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COMPREHENSIVE
CANCER CENTER

# DNA damage response and repair pathways and targets (in genitourinary malignancies)

Mamta Parikh, MD,MS

August 2023

California Cancer Consortium meeting

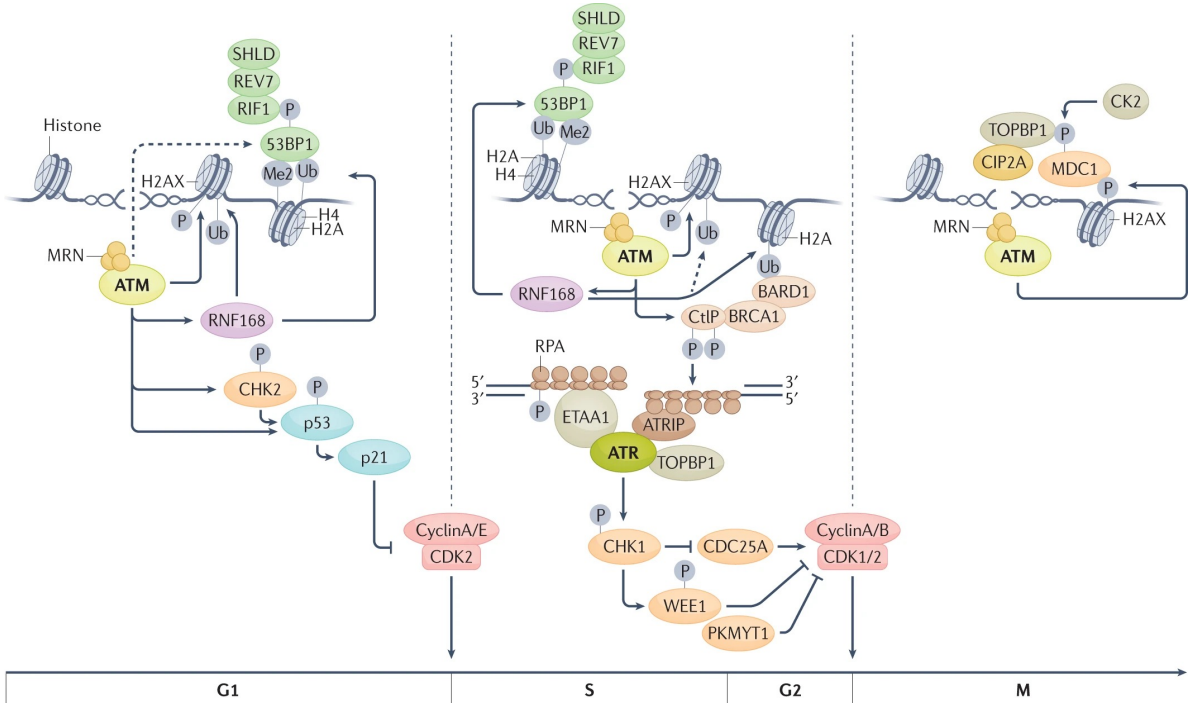
# Outline

- Overview of DNA damage pathways
- Case studies in Genitourinary Oncology
  - PARP inhibition in prostate cancer
  - PARPi in combination
  - ATR inhibitors in urothelial carcinoma
  - DNA damage response and repair mutations as biomarkers in urothelial carcinoma
- Future directions

# DNA damage and response/repair

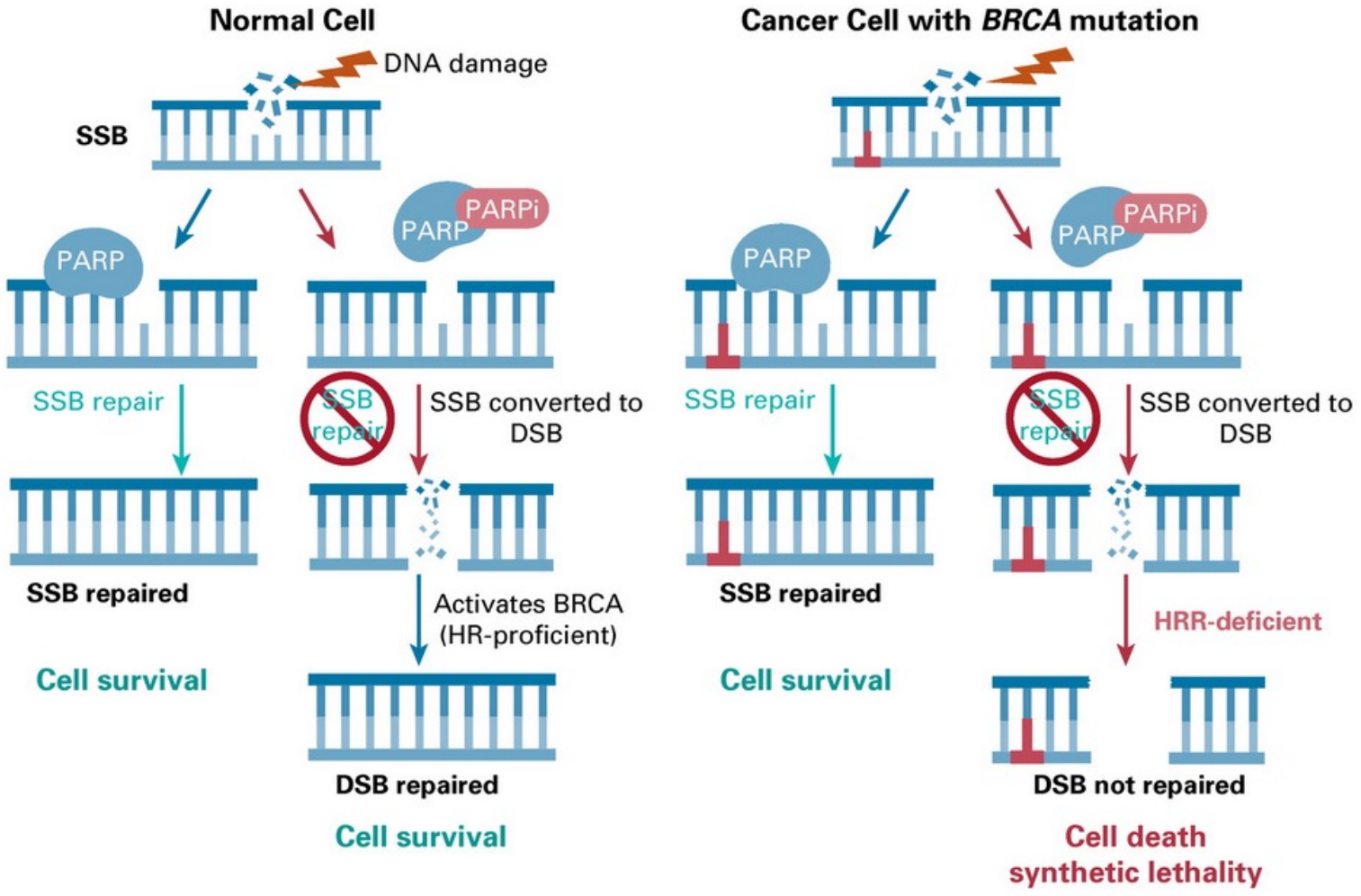

← multiple mechanisms for DNA damage

Countless mechanisms for DNA damage response and repair →



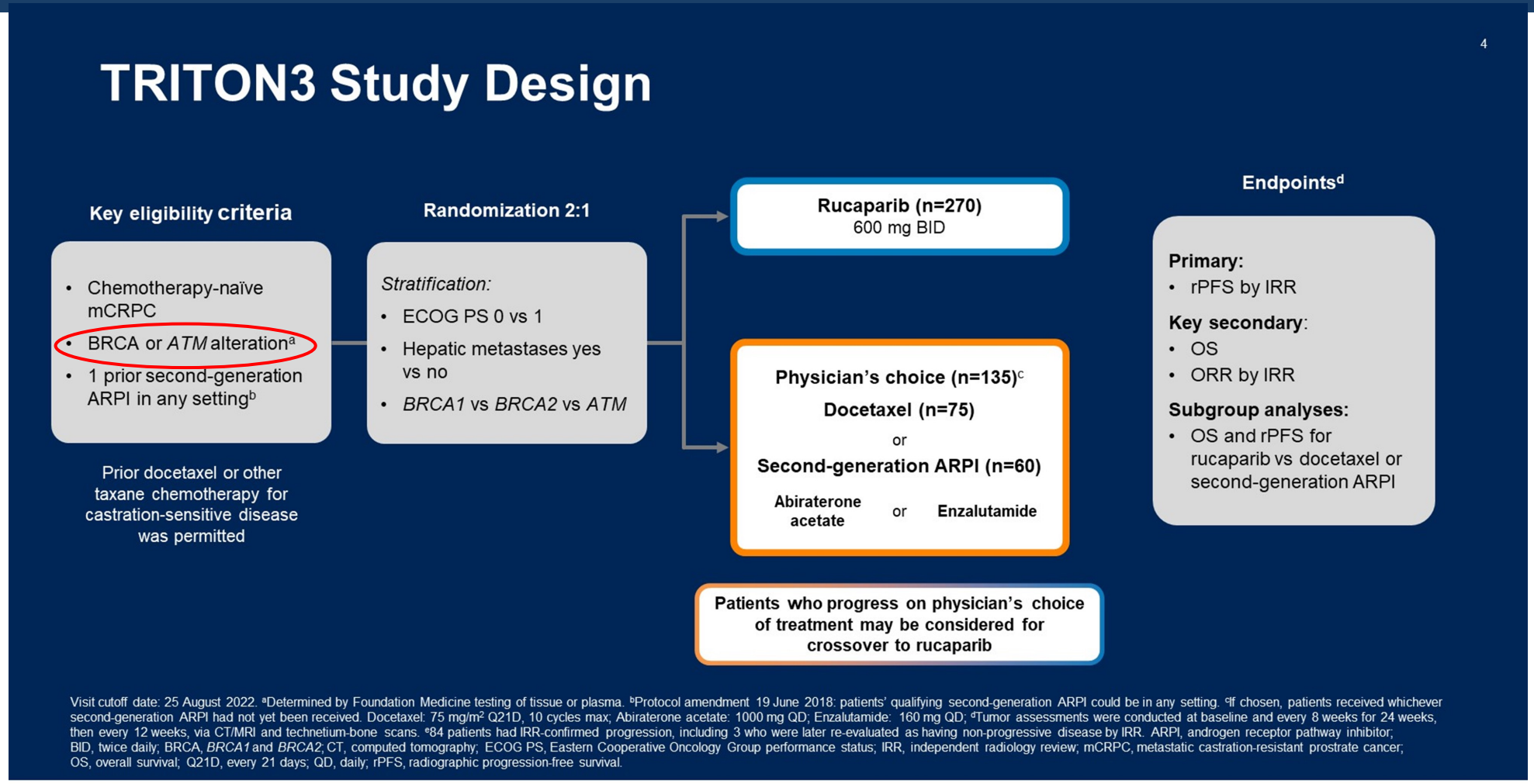

Groelly et al, *Nat Rev Cancer* 2023

# PARP inhibition and synthetic lethality



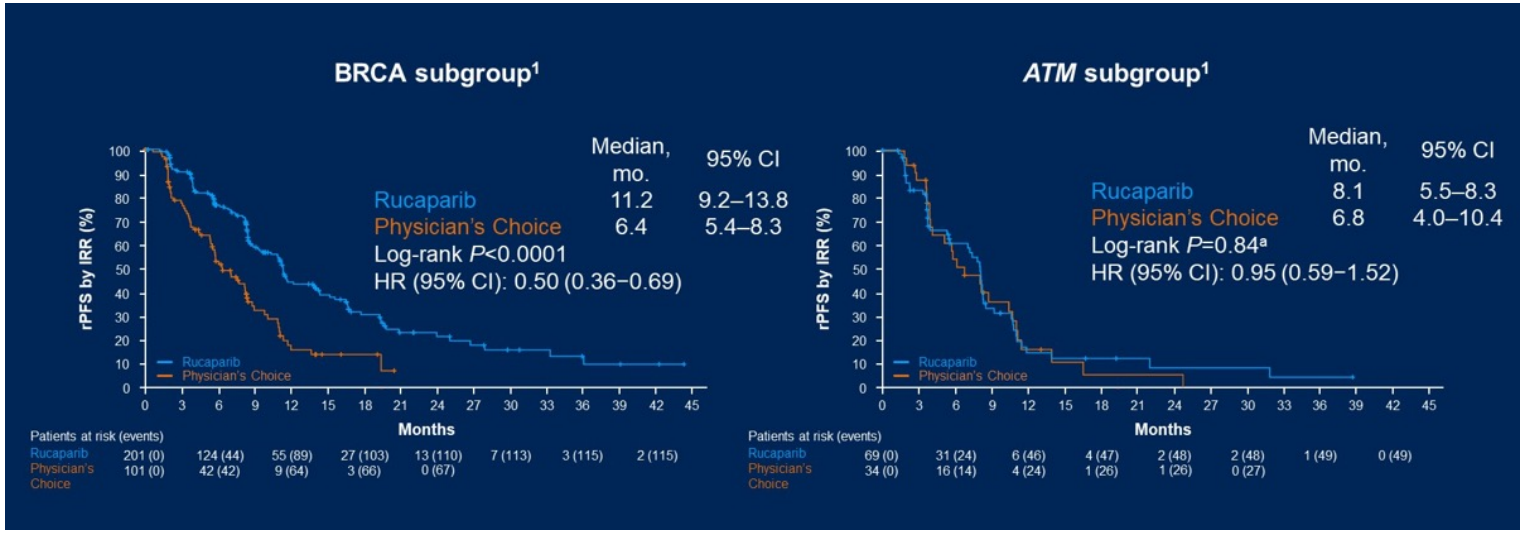

von Werdt et al, *JCO Precision Oncology* 2021

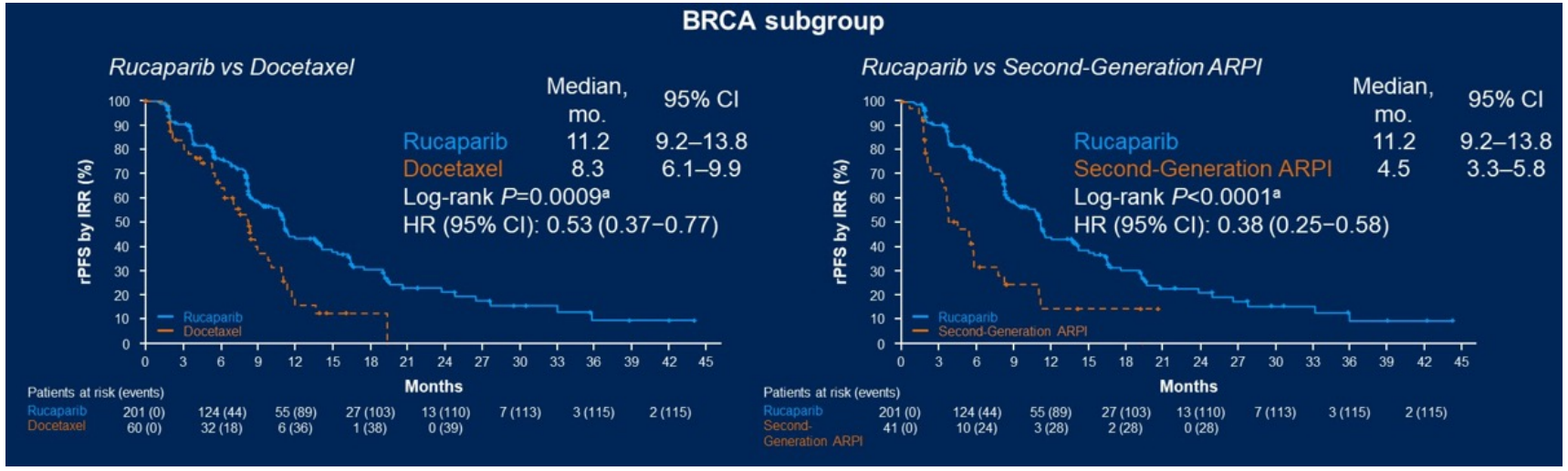
# PARP inhibition in castration-resistant prostate cancer



# Radiographic PFS results of TRITON3

- Benefit seen more in patients with BRCA alterations
- Benefit in comparison to taxane or AR pathway inhibitor

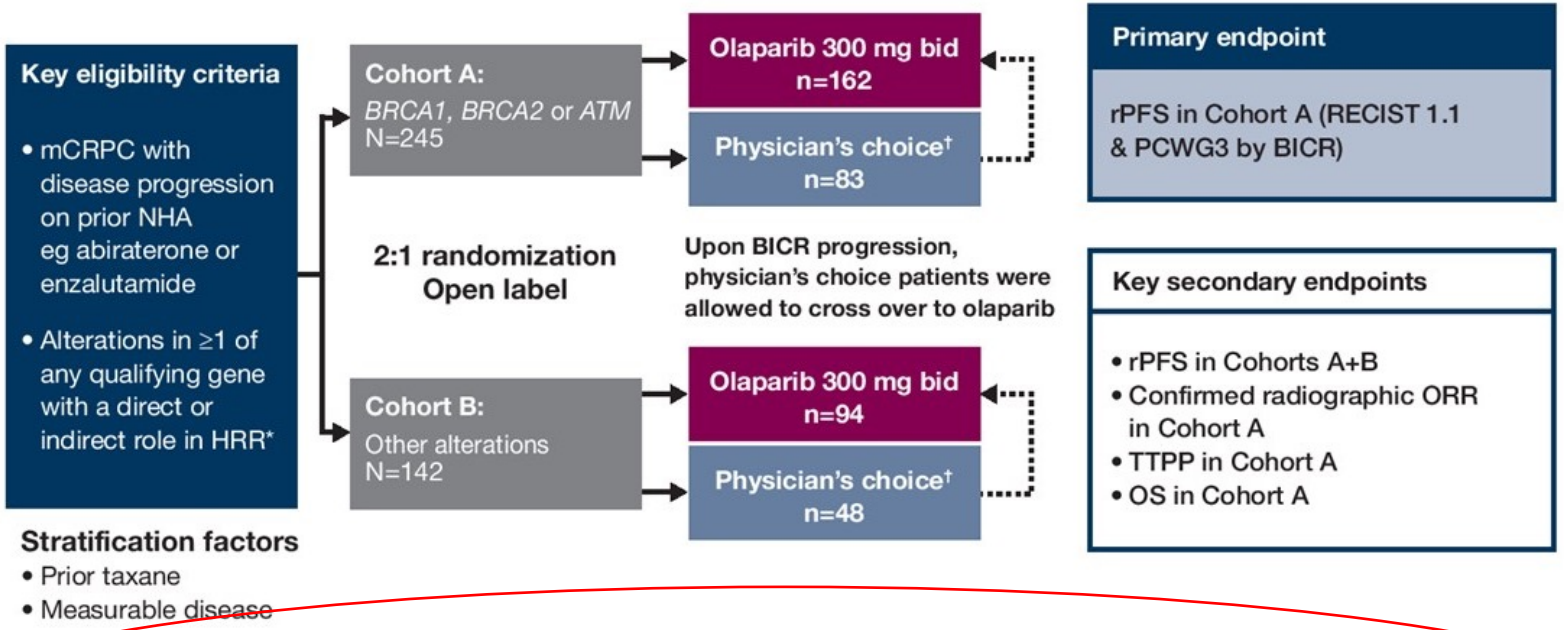



AH Bryce, ASCO GU 2023

# PARP inhibition in castration-resistant prostate cancer

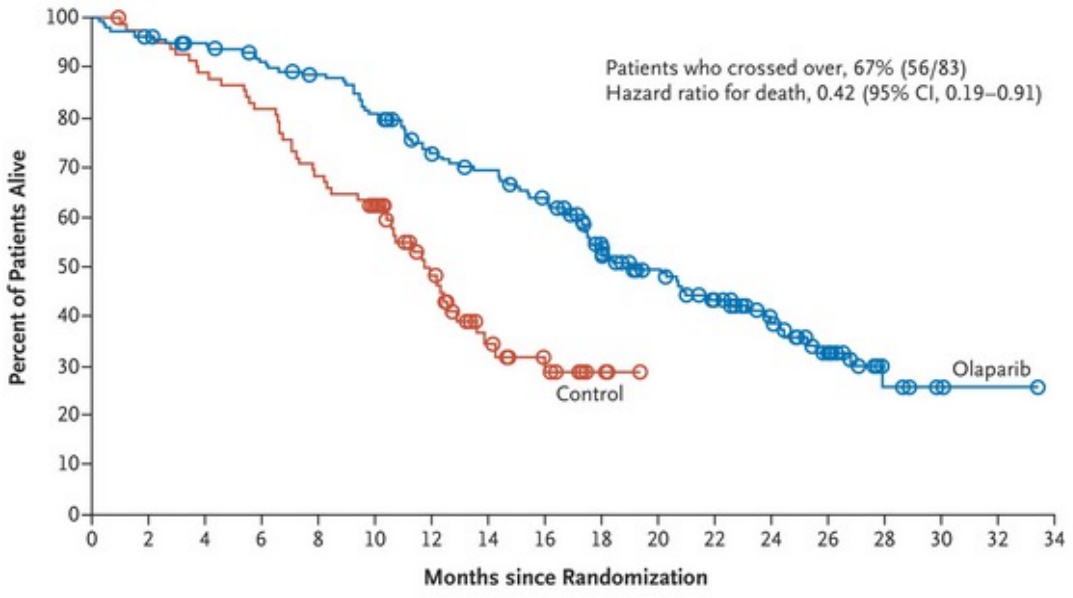
## PROfound Phase III Study Design



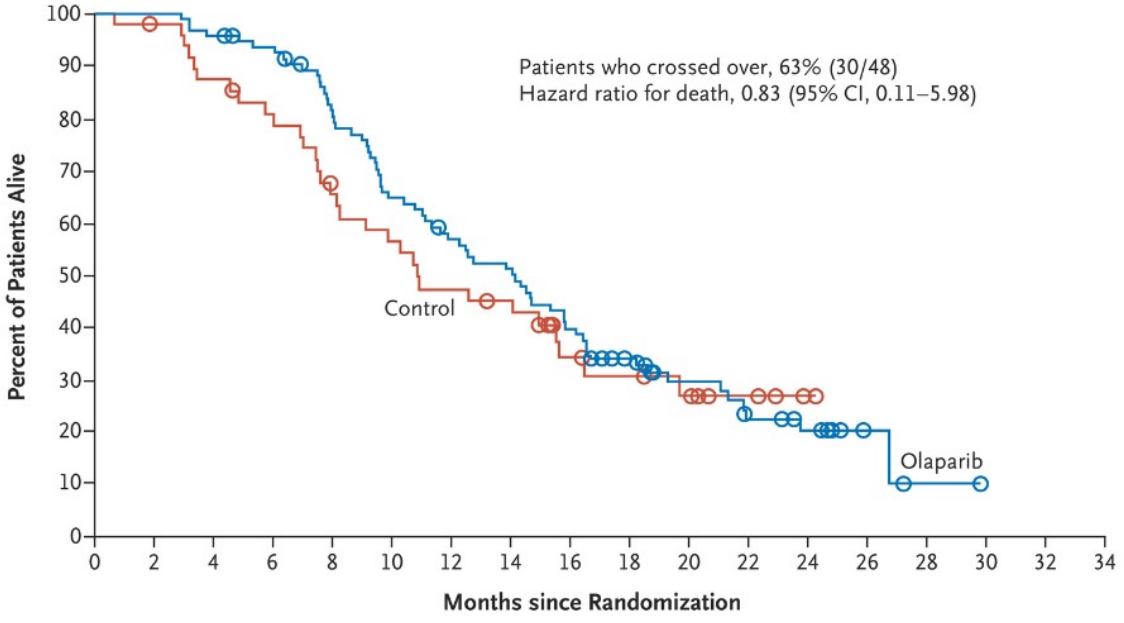

*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L*;
†Either enzalutamide (160 mg qd) or abiraterone (1000 mg qd plus prednisone [5 mg bid]). BICR, blinded independent central review; ORR, objective response rate; OS, overall survival; qd, once daily; TTPP, time to pain progression

# Efficacy results of PROfound

Crossover-adjusted overall survival
Cohort A (BRCA, ATM)




Crossover-adjusted overall survival
Cohort B (other alterations)



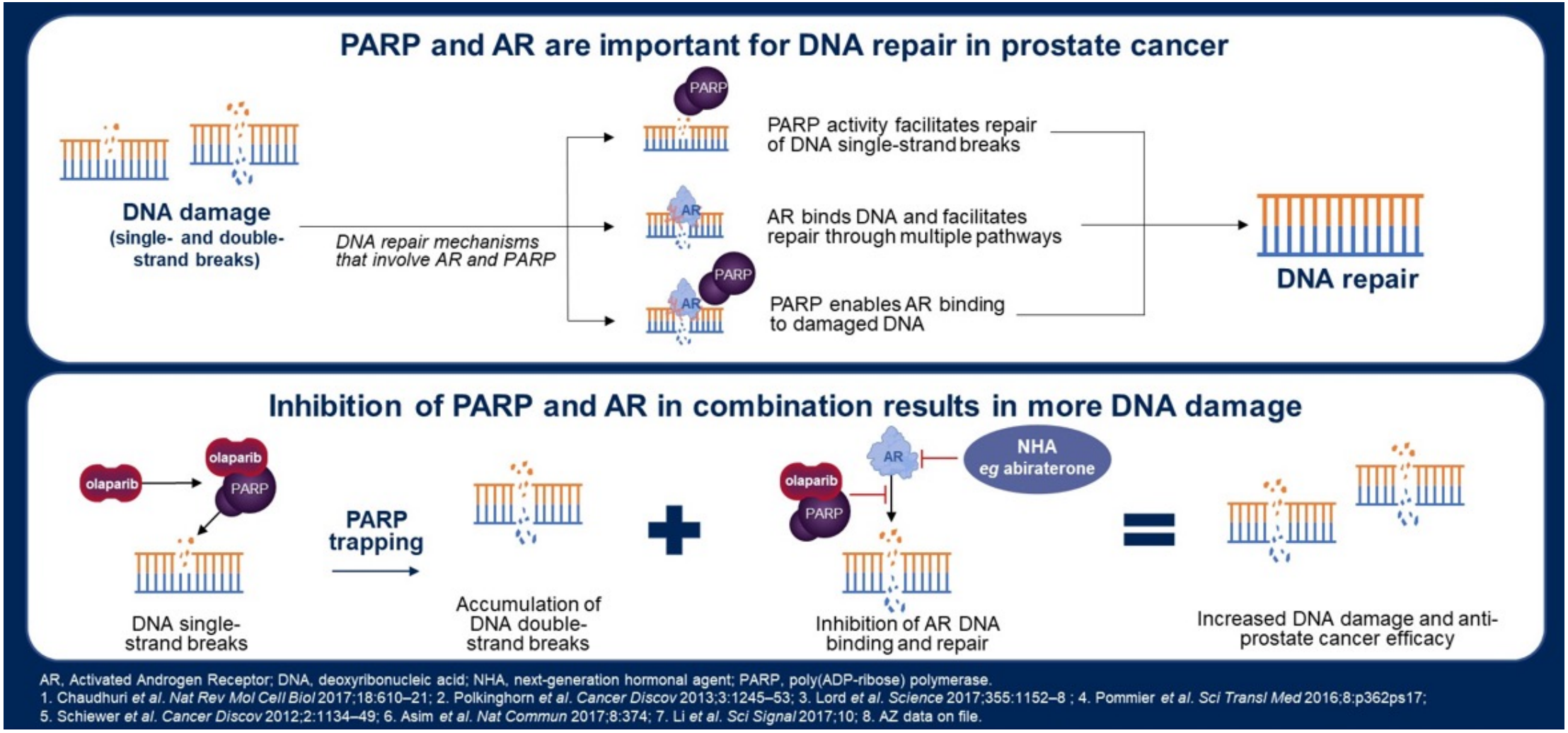

M Hussain *et* al N Engl J Med 2020

# Class Safety Effects of PARPi

- TRITON3 (rucaparib)
  - Grade 3+ anemia: 24%
  - All grade nausea: 50%
  - All grade fatigue: 61%

- PROfound (olaparib)
  - Grade 3+ anemia: 21%
  - All grade nausea: 41%
  - All grade fatigue: 41%

# Rationale for combination approaches in prostate cancer




AR, Activated Androgen Receptor; DNA, deoxyribonucleic acid; NHA, next-generation hormonal agent; PARP, poly(ADP-ribose) polymerase.

1. Chaudhuri *et al. Nat Rev Mol Cell Biol* 2017;18:610–21; 2. Polkinghorn *et al. Cancer Discov* 2013;3:1245–53; 3. Lord *et al. Science* 2017;355:1152–8 ; 4. Pommier *et al. Sci Transl Med* 2016;8:p362ps17; 5. Schiewer *et al. Cancer Discov* 2012;2:1134–49; 6. Asim *et al. Nat Commun* 2017;8:374; 7. Li *et al. Sci Signal* 2017;10; 8. AZ data on file.

N Clarke, ASCO GU 2023

# PROpel: Phase III trial design

**Patient population**

- 1L mCRPC
- **Asymptomatic, mildly symptomatic, symptomatic**
- No prior abiraterone
- **Other NHAs allowed if stopped ≥12 months prior to enrollment**
- ECOG 0–1

**Stratification factors**

- Site of distant metastases: bone only vs visceral vs other
- Prior taxane at mHSPC: yes vs no

1:1

**Abiraterone 1000 mg qd* + olaparib 300 mg bid**
n=399
**Full dose of abiraterone and olaparib**

**Abiraterone 1000 mg qd* + placebo**
n=397
**Full dose of abiraterone**

**Primary endpoint**

- rPFS by investigator assessment (sensitivity analysis by blinded independent central review)

**Key secondary endpoint**

- OS

**Additional preplanned analyses:**

- TFST
- PFS2
- HRQoL
- HRRm status (by tissue and ctDNA after randomization and before primary analysis; see supplement)
- Safety and tolerability

**Analysis timeline:**

**DCO1: 30 July 2021**
rPFS (primary)

**DCO2: 14 March 2022**
OS (interim)

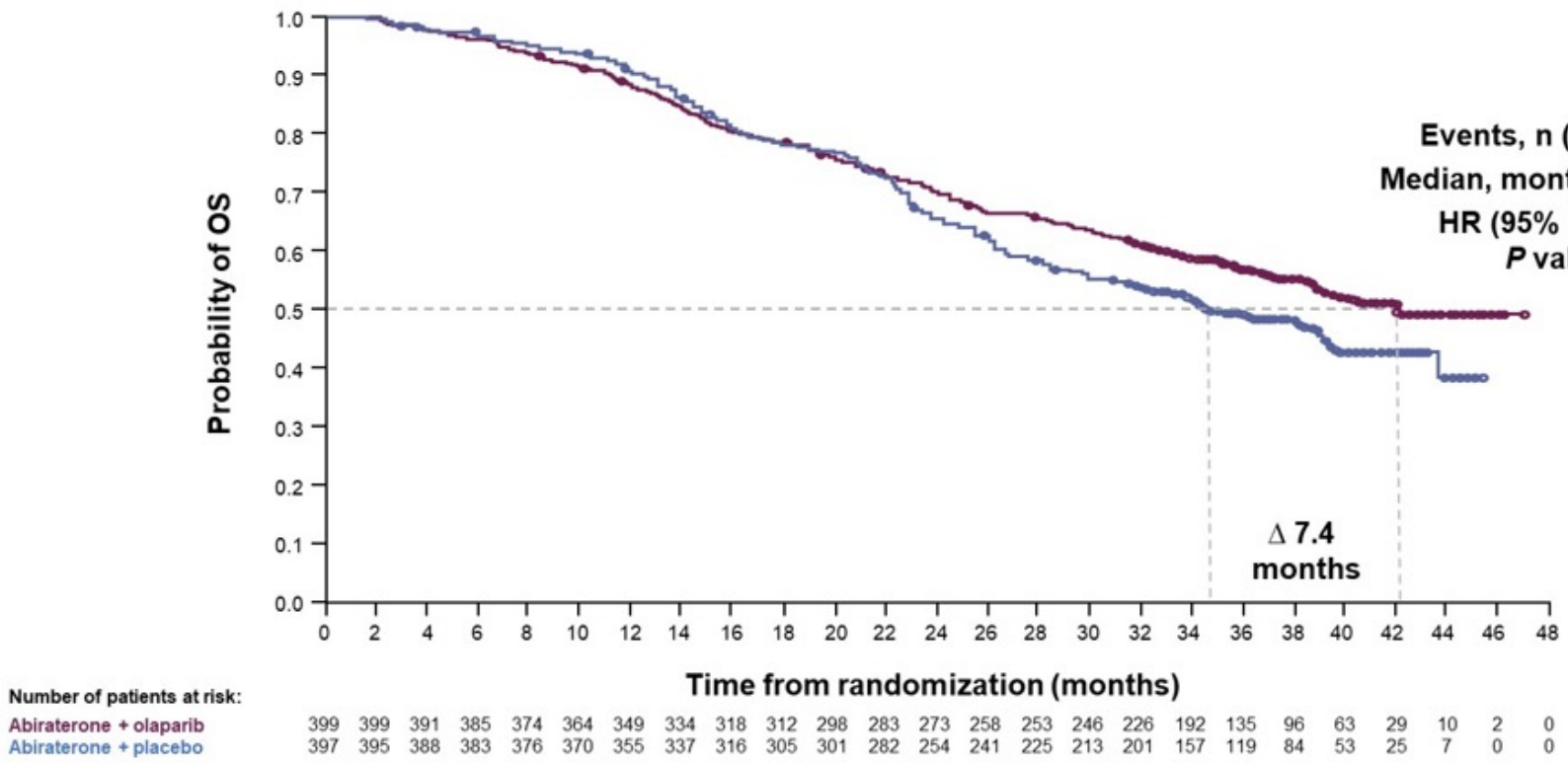
**DCO3: 12 October 2022**
OS (final pre-specified)
*current dataset*

*In combination with prednisone or prednisolone 5 mg bid.
bid, twice daily; ctDNA, circulating tumor DNA; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; HRRm, homologous recombination repair mutation; HRQoL, health-related quality of life; mHSPC, metastatic hormone-sensitive prostate cancer; PFS2, time to second progression or death; qd, once daily; TFST, time to first subsequent therapy or death.



PRESENTED BY: Professor Noel Clarke

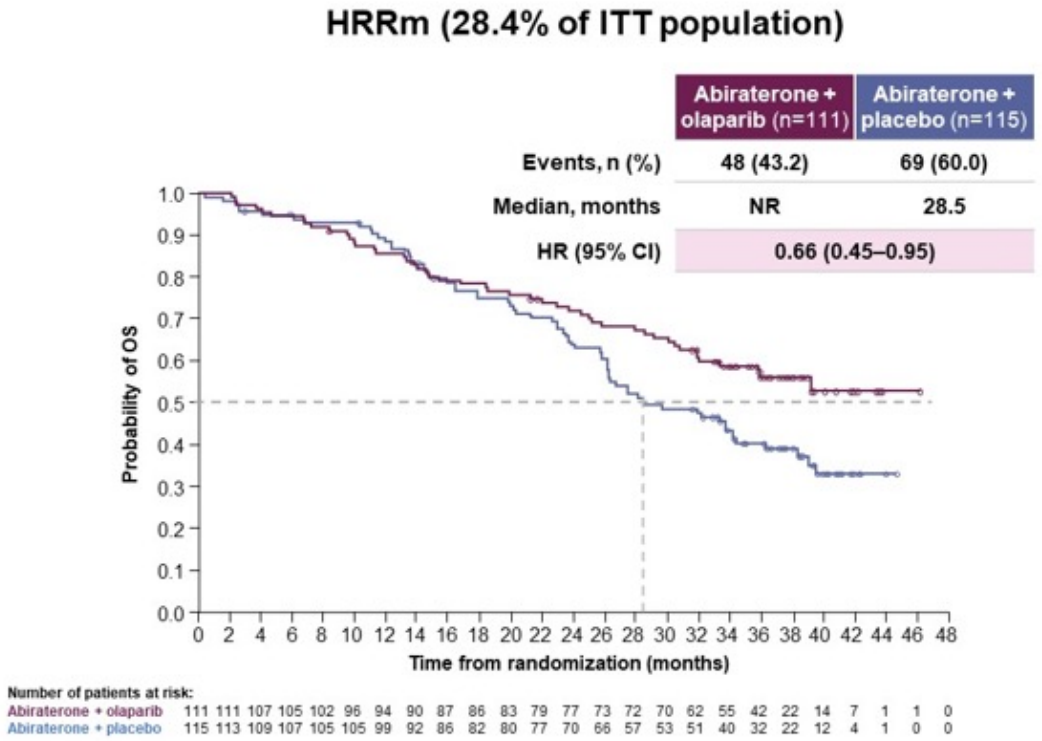
# PROpel Overall Survival results in ITT population

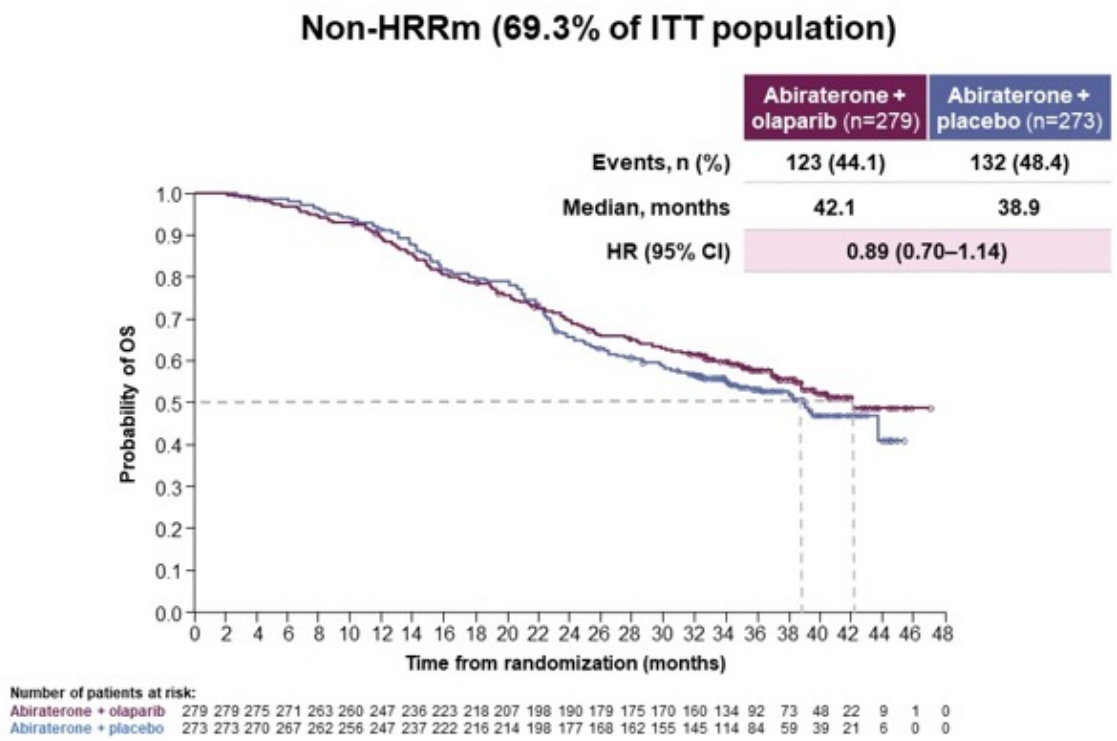



| | Abiraterone + olaparib (n=399) | Abiraterone + placebo (n=397) |
|---|---|---|
| Events, n (%) | 176 (44.1) | 205 (51.6) |
| Median, months | 42.1 | 34.7 |
| HR (95% CI) | 0.81 (0.67–1.00) | |
| *P* value | 0.0544 | |
| 2-sided boundary for significance | 0.0377 | |
| | 47.9% maturity | |

N Clarke, ASCO GU 2023

# PROpel: OS results based on HRRm status

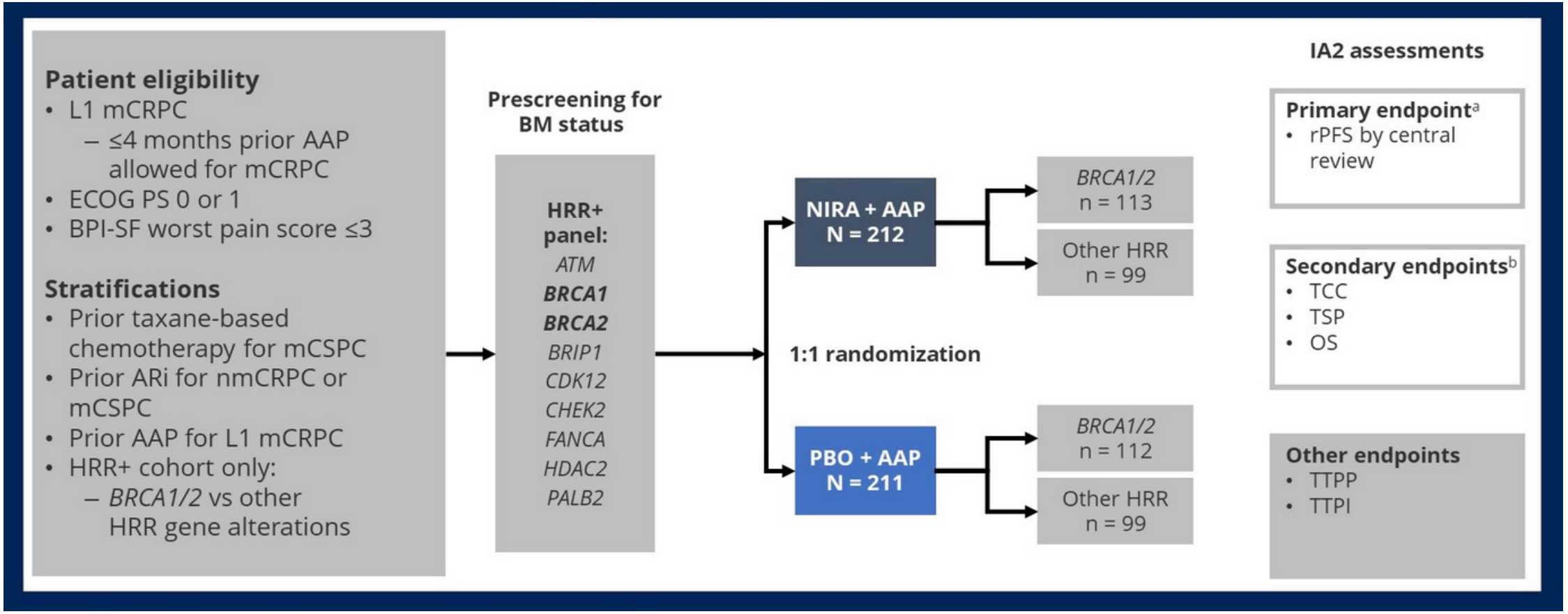



- BRCAm ~12% of abiraterone + olaparib arm and ~10% of abiraterone + placebo arm

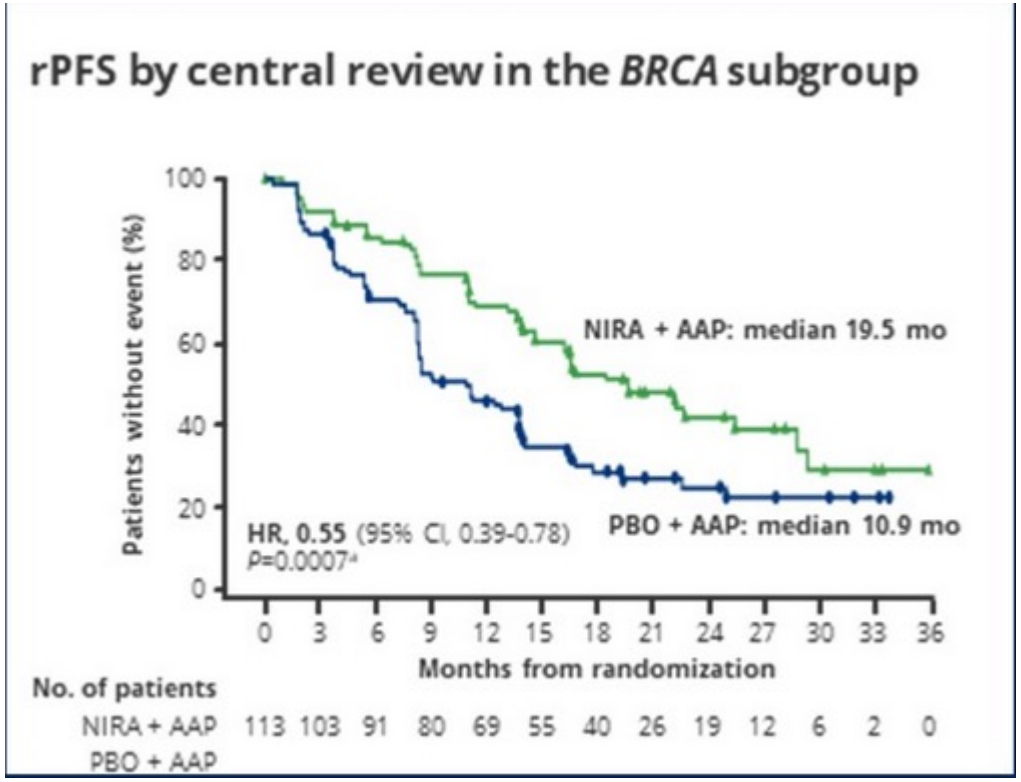
N Clarke, ASCO GU 2023

# MAGNITUDE: Phase III trial design




Efstathiou, ASCO GU 2023

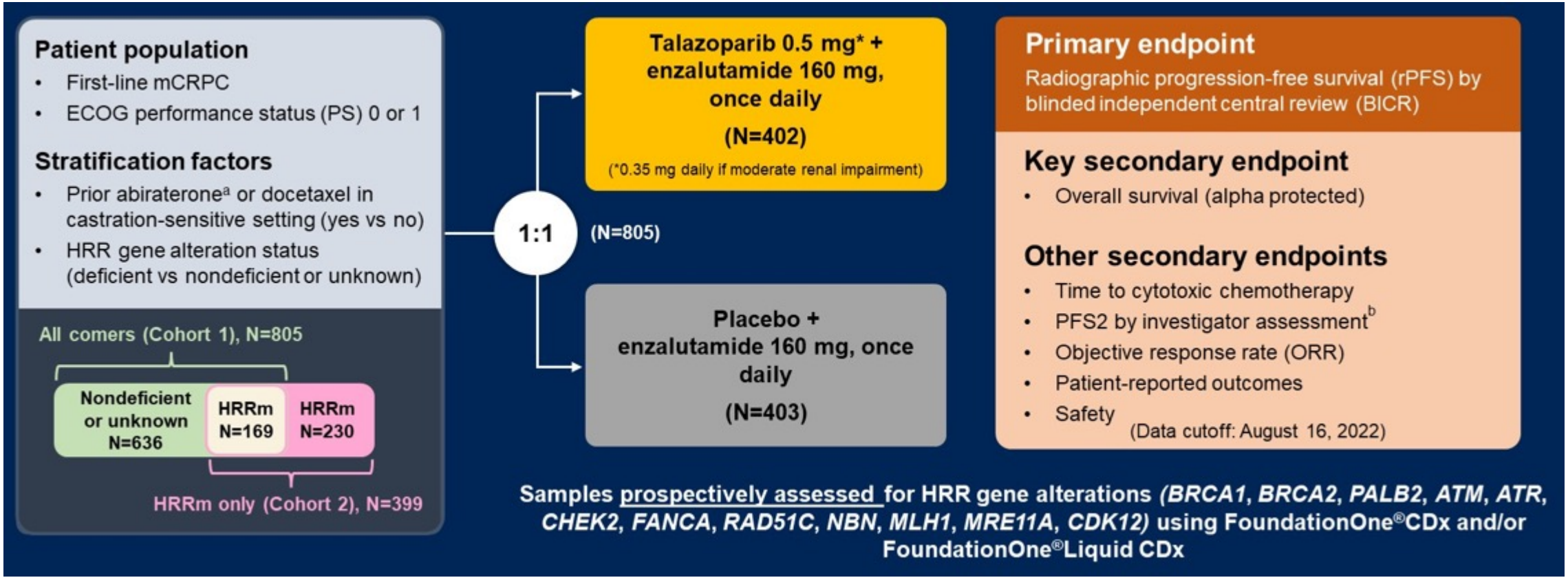
# MAGNITUDE primary endpoint results




- BRCA1/2: 53% of patients in both arms
- Time to initiation of cytotoxic chemotherapy in BRCA subgroup was improved in niraparib + abiraterone arm (not reached vs 27.3 months, HR: 0.56, p=0.0152)
- No statistically significant difference in overall survival in BRCA subgroup

Efstathiou, ASCO GU 2023

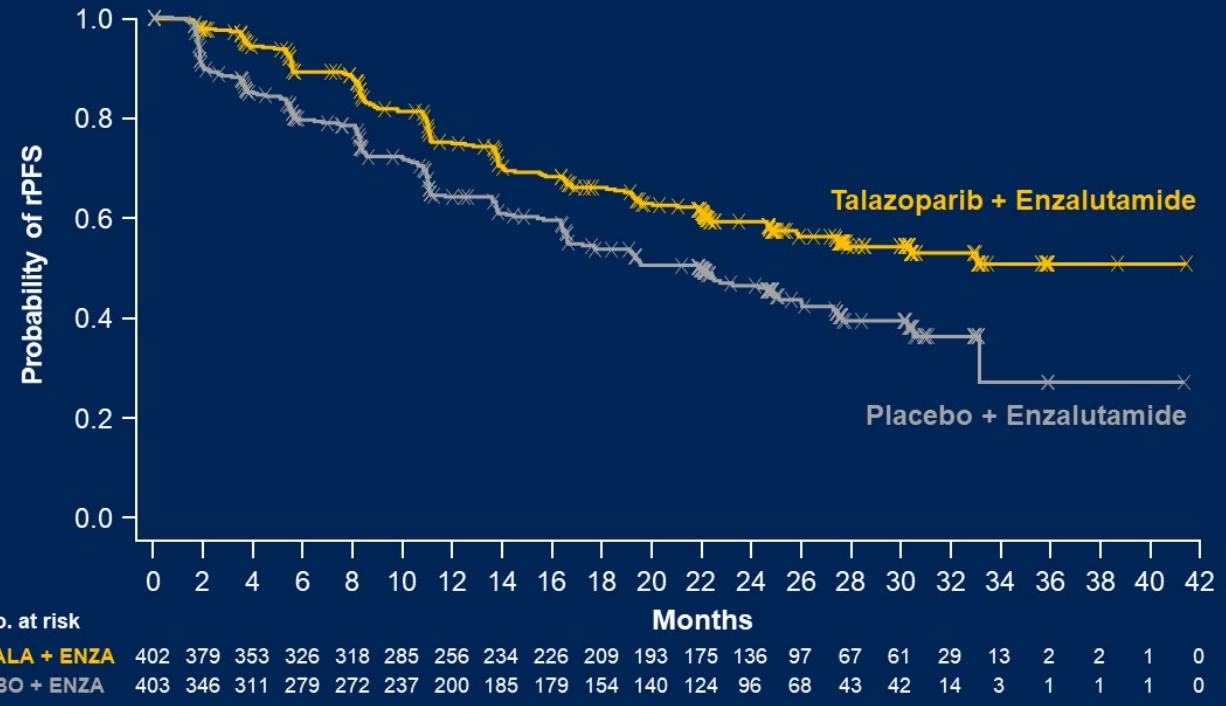
# TALAPRO-2 Phase III trial design




Agarwal, ASCO GU 2023

# TALAPRO-2 Primary Endpoint: rPFS by BICR

Treatment with talazoparib plus enzalutamide resulted in a 37% reduced risk of progression or death




| | TALA + ENZA (N=402) | PBO + ENZA (N=403) |
|---|---|---|
| Events, n | 151 | 191 |
| Median (95% CI), months | Not reached (NR) (27.5–NR) | 21.9 (16.6–25.1) |
| HR (95% CI) | 0.63 (0.51–0.78); *P* < 0.001 | |

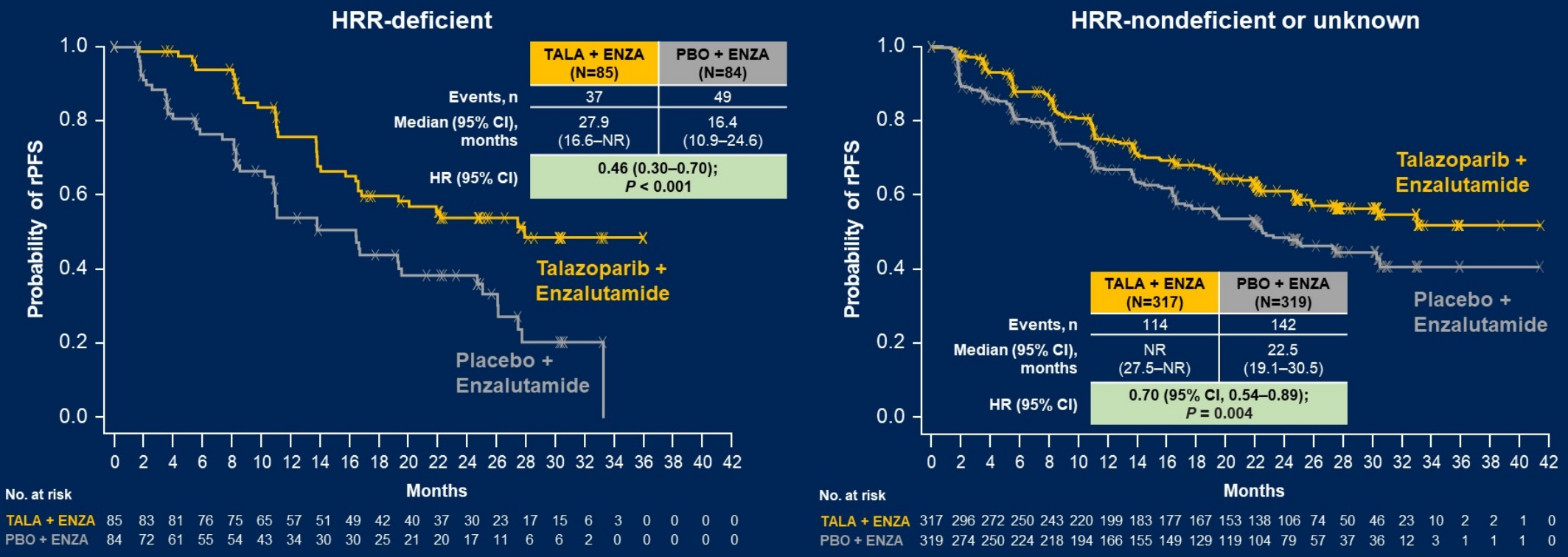
**Median follow-up for rPFS was 24.9 and 24.6 months, respectively**

A consistent treatment effect was seen for investigator-assessed rPFS: HR 0.64 (95% CI, 0.50–0.81); *P* < 0.001

**Stratified hazard ratios (HRs) and 2-sided *P* values are reported throughout this presentation unless otherwise stated.**

# TALAPRO-2: rPFS by BICR by HRR Status

A clinically meaningful reduction in risk of progression or death was seen regardless of HRR status




HRR gene alteration status (deficient vs nondeficient or unknown) as a stratification factor.

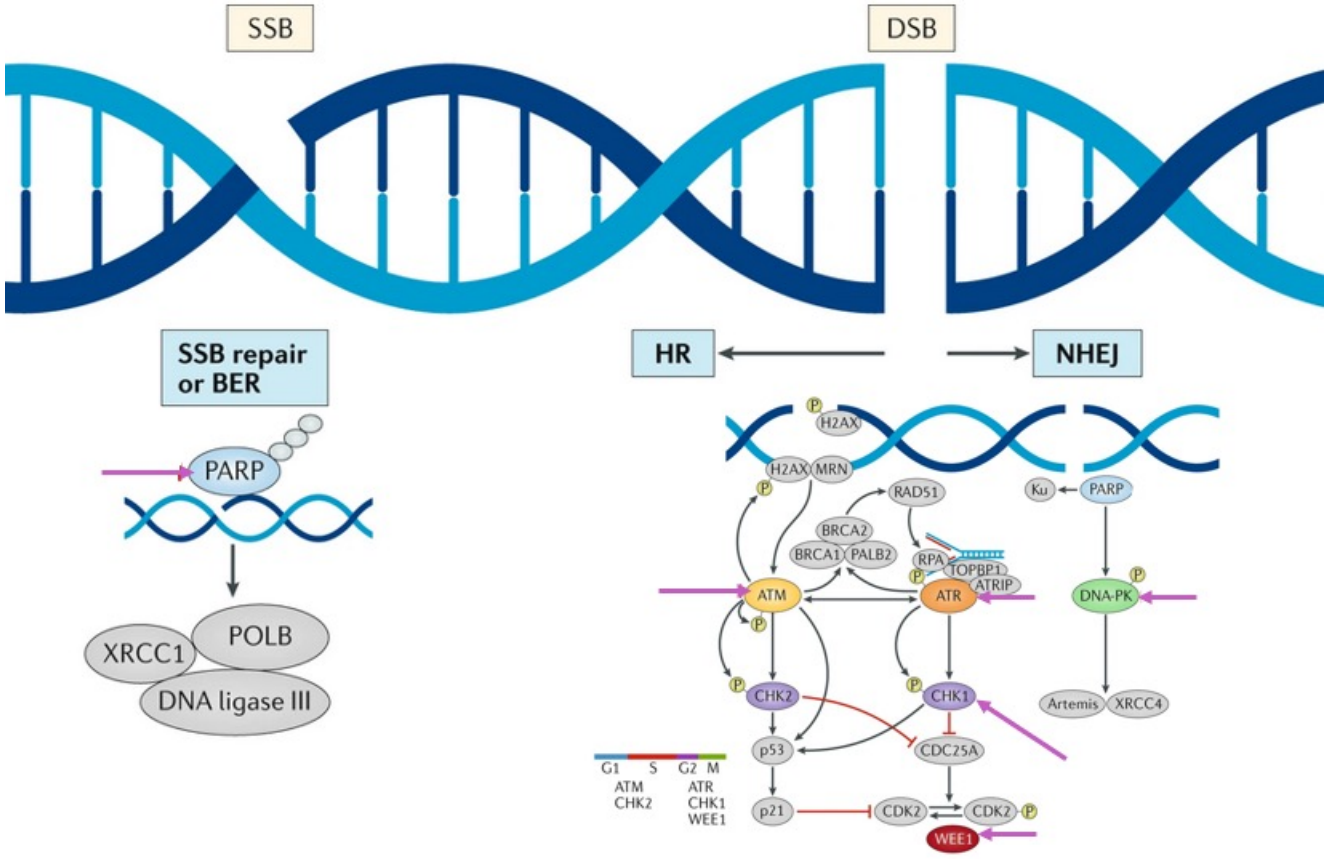
# Verdict on combination therapy approaches?

- Appear to benefit those with HRRm most significantly

- FDA approvals of:
  - olaparib + abiraterone + prednisone → BRCAm
  - niraparib + abiraterone + prednisone → BRCAm
  - talazoparib + enzalutamide → HRRm (ATM, ATR, BRCA1, BRCA2, CDK12, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C)
  - CASPAR trial of enzalutamide + rucaparib vs enzalutamide + placebo is ongoing

- Other combination approaches:
  - olaparib + pembrolizumab (Ph II KEYLNK-010) vs abiraterone or enzalutamide- no improvement in rPFS or OS
  - PHII-180 (COMRADE) : evaluating Radium-223 +/- olaparib in patients with mCRPC, currently enrolling
  - LuPARP: olaparib + $^{177}$-Lu-PSMA-617

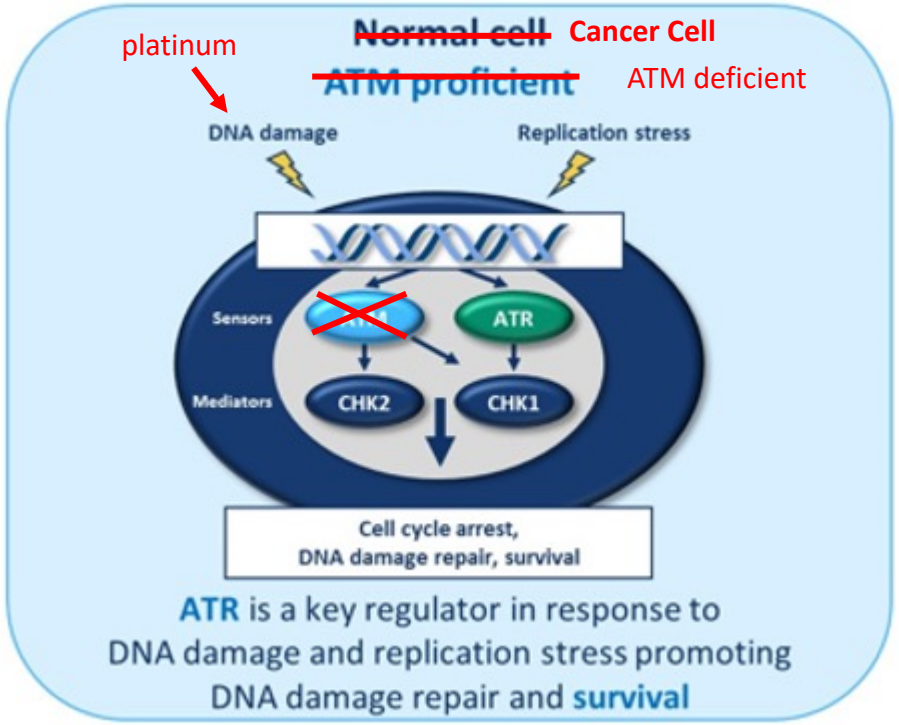
# Beyond PARP inhibition




- Some patients do not respond to PARPi's
- Resistance also develops
- Potential downstream targets (ATR, ATM, CK1, WEE1, DNA-PK)

Pilie *et al Nature Reviews Clinical Oncology* 2019

# ATR inhibition in bladder cancer



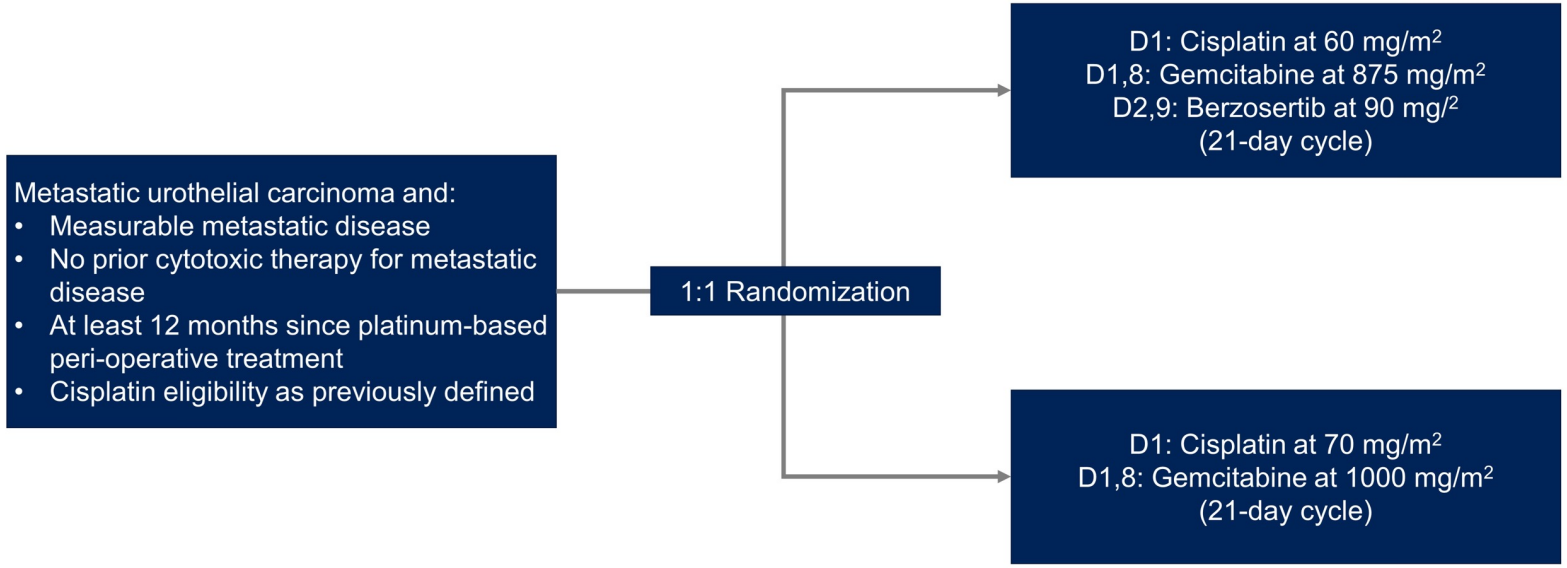

- Cancer cells treated with platinum-based chemotherapy
  - Leads to cell cycle arrest, but triggers DDR mechanisms
    → Transient induction of ATR activity
  - ATM deficient cancer cells
    → primed for synthetic lethality with ATR inhibition
  - Preclinical models suggest cisplatin and ATRi are synergistic in lung and bladder cancer

Hall *et al*, *Oncotarget* 2014
Vendetti *et al*, *Oncotarget* 2015

# PHII-135



## Study Design

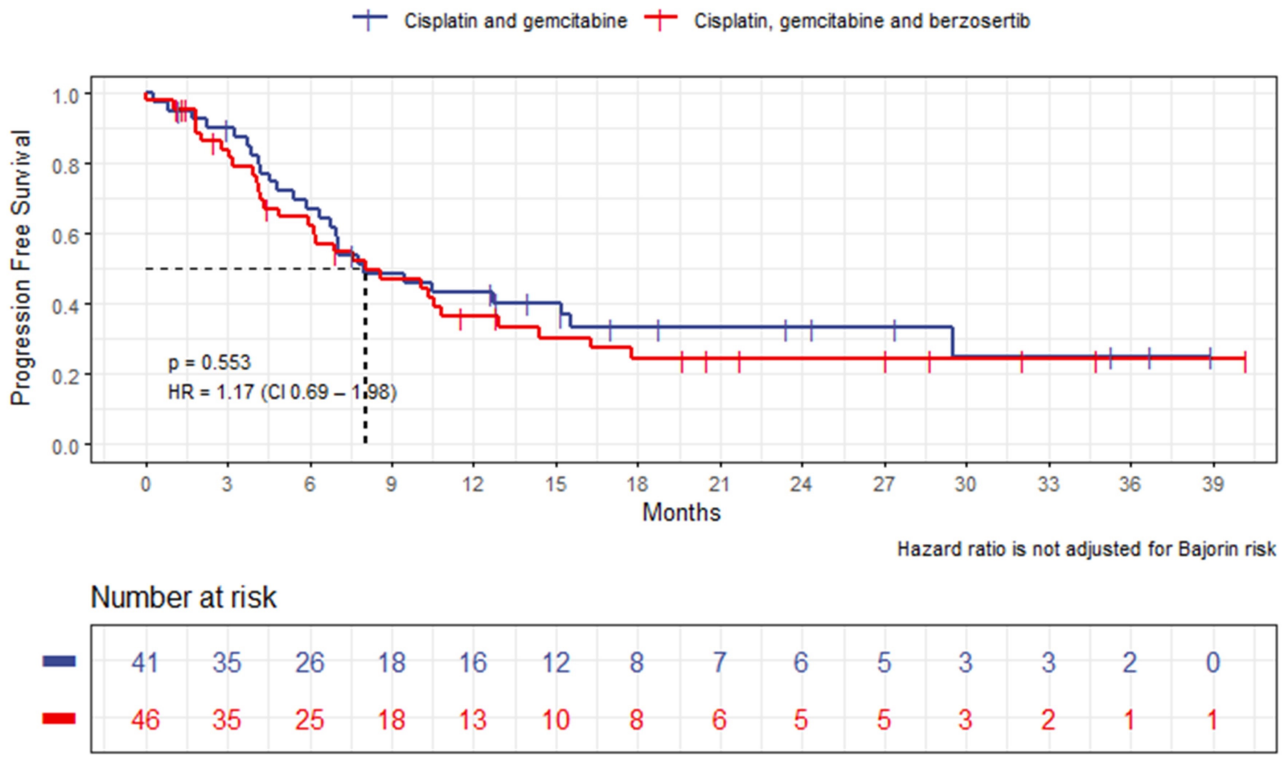



Primary endpoint: PFS

- Patients stratified by Bajorin risk group
- Treatment continued up to 6 cycles on each study arm

Presented By: **Sumanta K. Pal, MD, FASCO**
**City of Hope Comprehensive Cancer Center**

# Results: Progression-Free Survival



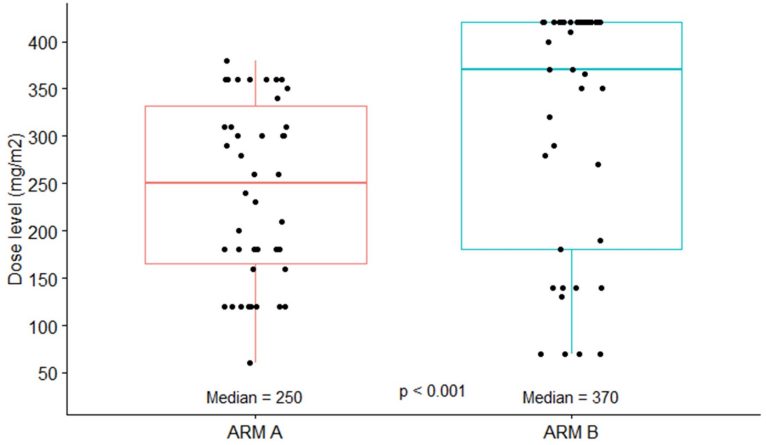

Median PFS was 8.0 months on both study arms.

Presented By: **Sumanta K. Pal, MD, FASCO**
**City of Hope Comprehensive Cancer Center**

# Effect of toxicity from ATRi in combination with chemotherapy

| | Cisplatin, gemcitabine and berzosertib (N=46) | Cisplatin and gemcitabine (N=41) |
|---|---|---|
| **Patients requiring dose reduction for:** | | |
| **Cisplatin** | 16 (34.8%) | 14 (34.2%) |
| **Gemcitabine** | 28 (60.9%) | 22 (53.7%) |
| **Berzosertib** | 9 (19.6%) | N/A |
| **Use of growth factors** | 23 (50%) | 14 (34.1%) |

## Results: Cumulative Dosing of Cisplatin



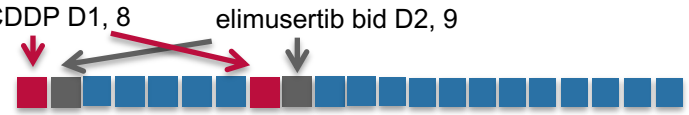

- Patients receiving berzosertib (Arm A) had a median cisplatin dose of 250 mg/m$^2$ (intended dose: 360 mg/m$^2$); significantly lower than the median dose of 370 mg/m$^2$ (intended dose: 420 mg/m$^2$) on the control arm (Arm B) (P<0.001)

**Hematologic toxicities of combination vs gem/cis:**

Grade 3 thrombocytopenia: 22% both arms
Grade 4 thrombocytopenia: 37% vs 17%
Grade 3 neutropenia: 20% vs 22%
Grade 4 neutropenia: 17% vs 5%
Grade 3 anemia: 57% vs 24%

# PHII-179: currently enrolling

Advanced solid tumor patients
- ECOG 0-2
- <300 mg/m$^2$ prior cisplatin
- Adequate organ /hematologic function



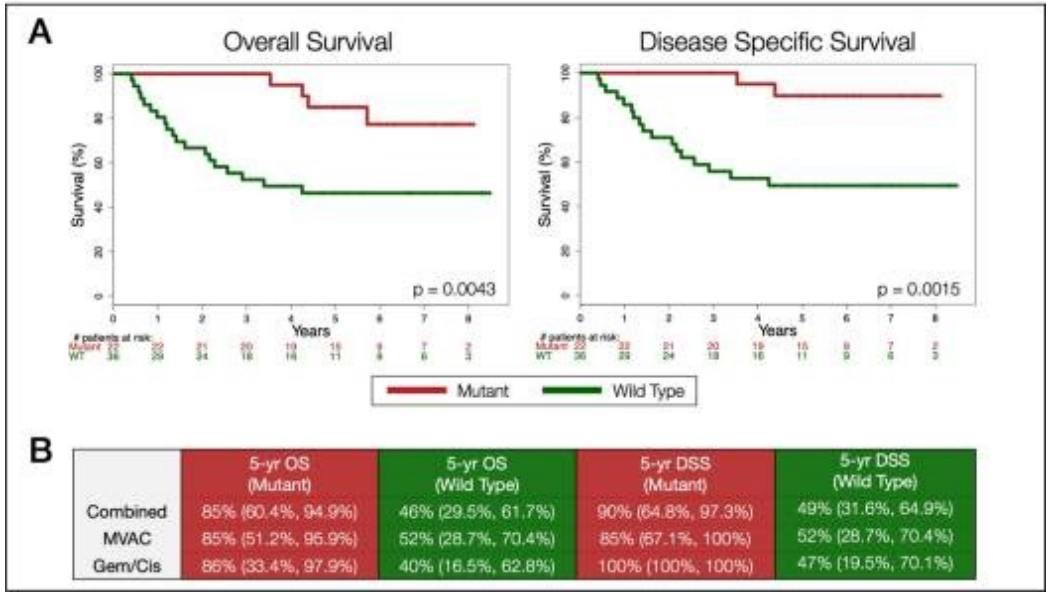

Cisplatin IV D1, D8
elimusertib PO D2, 9
Cycle = 21 days

| Revised dose levels | |
|---|---|
| DL -2a | Cisplatin 30 mg/m$^2$ D1, 8<br>elimusertib 10 mg PO qd D2 |
| DL -1a | Cisplatin 30 mg/m$^2$ D1, 8<br>elimusertib 20 mg PO qd D2 |
| DL 0a | Cisplatin 30 mg/m$^2$ D1, D8<br>elimusertib 20 mg PO qd D2, 9 |
| DL +1 | Cisplatin 35 mg/m$^2$<br>elimusertib 20 mg PO bid D2, 9 |
| DL +2 | Cisplatin 35 mg/m2 D1, 8<br>elimusertib 30 mg PO bid D2, 9 |
| DL +3 | Cisplatin 35 mg/m2 D1, 8<br>elimusertib 40 mg PO bid D2, 9 |

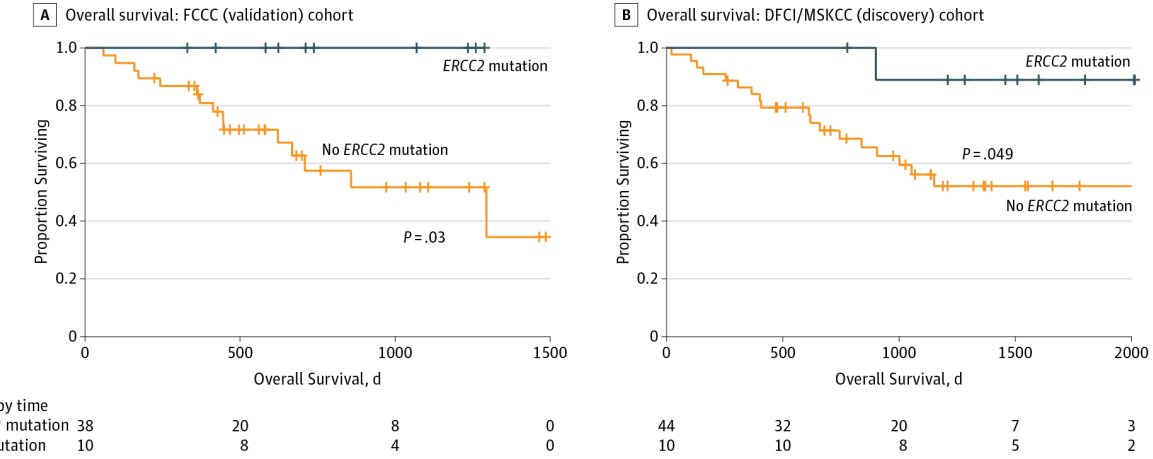
Doublet RP2D – to inform starting dose level of cohort of patients treated with elimusertib + gemcitabine + cisplatin

*Both PHII-135 and PHII-179 eligibility requirements are unselected patient populations → importance of ATM expression, DDR mutations unknown

# DDR as a biomarker in muscle-invasive bladder cancer




| | 5-yr OS (Mutant) | 5-yr OS (Wild Type) | 5-yr DSS (Mutant) | 5-yr DSS (Wild Type) |
|---|---|---|---|---|
| Combined | 85% (60.4%, 94.9%) | 46% (29.5%, 61.7%) | 90% (64.8%, 97.3%) | 49% (31.6%, 64.9%) |
| MVAC | 85% (51.2%, 95.9%) | 52% (28.7%, 70.4%) | 85% (67.1%, 100%) | 52% (28.7%, 70.4%) |
| Gem/Cis | 86% (33.4%, 97.9%) | 40% (16.5%, 62.8%) | 100% (100%, 100%) | 47% (19.5%, 70.1%) |




At least one mutation in ATM, RB1, FANCC (red) vs wildtype (green) → better OS/DSS

Miron *et al Eur Urol* 2019

(Further validated with S1314 study)

Plimack *et al* ASCO 2023

Presence or absence or ERCC2 mutation associated with better OS

Liu *et al JAMA Onc* 2016

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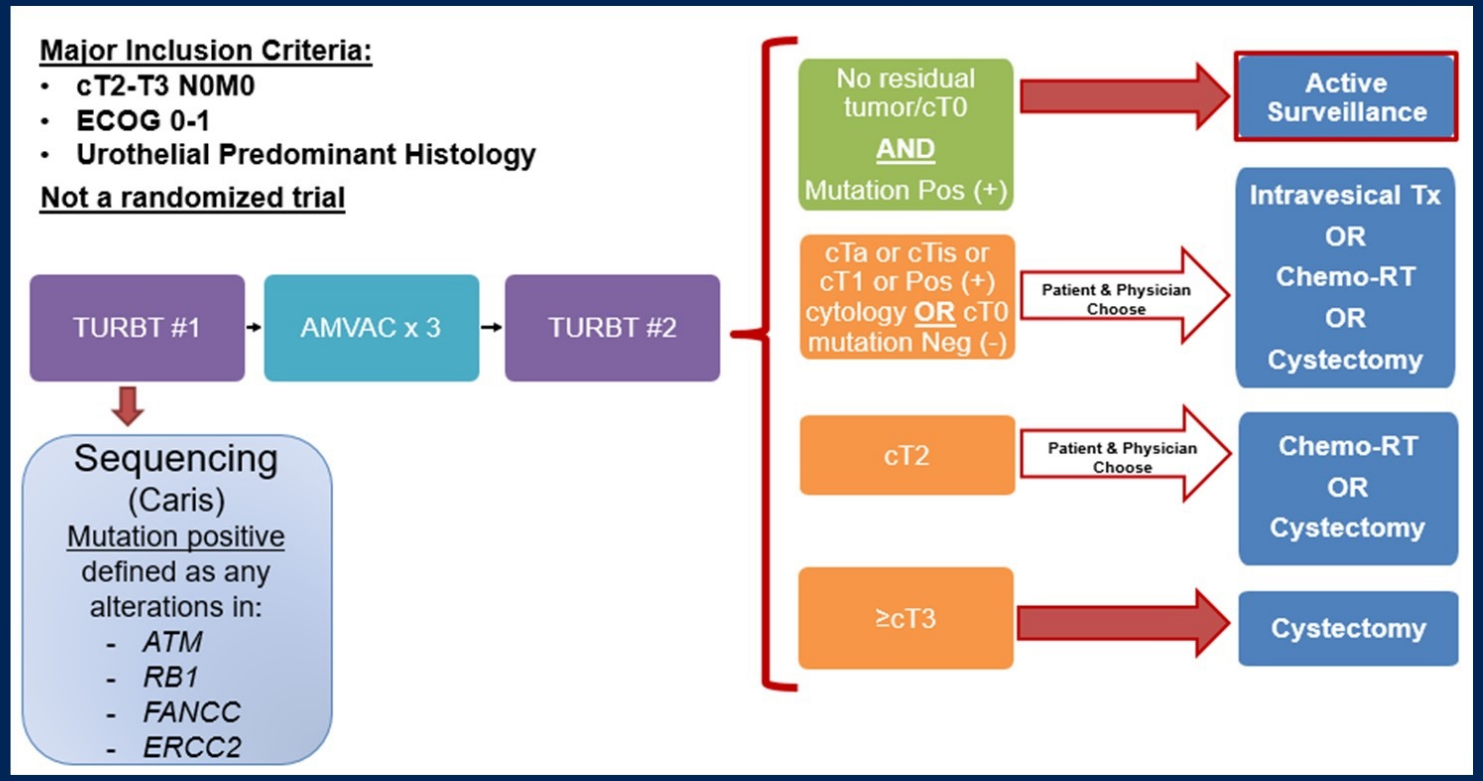
# RETAIN Bladder

## Trial Schema: NCT02710734



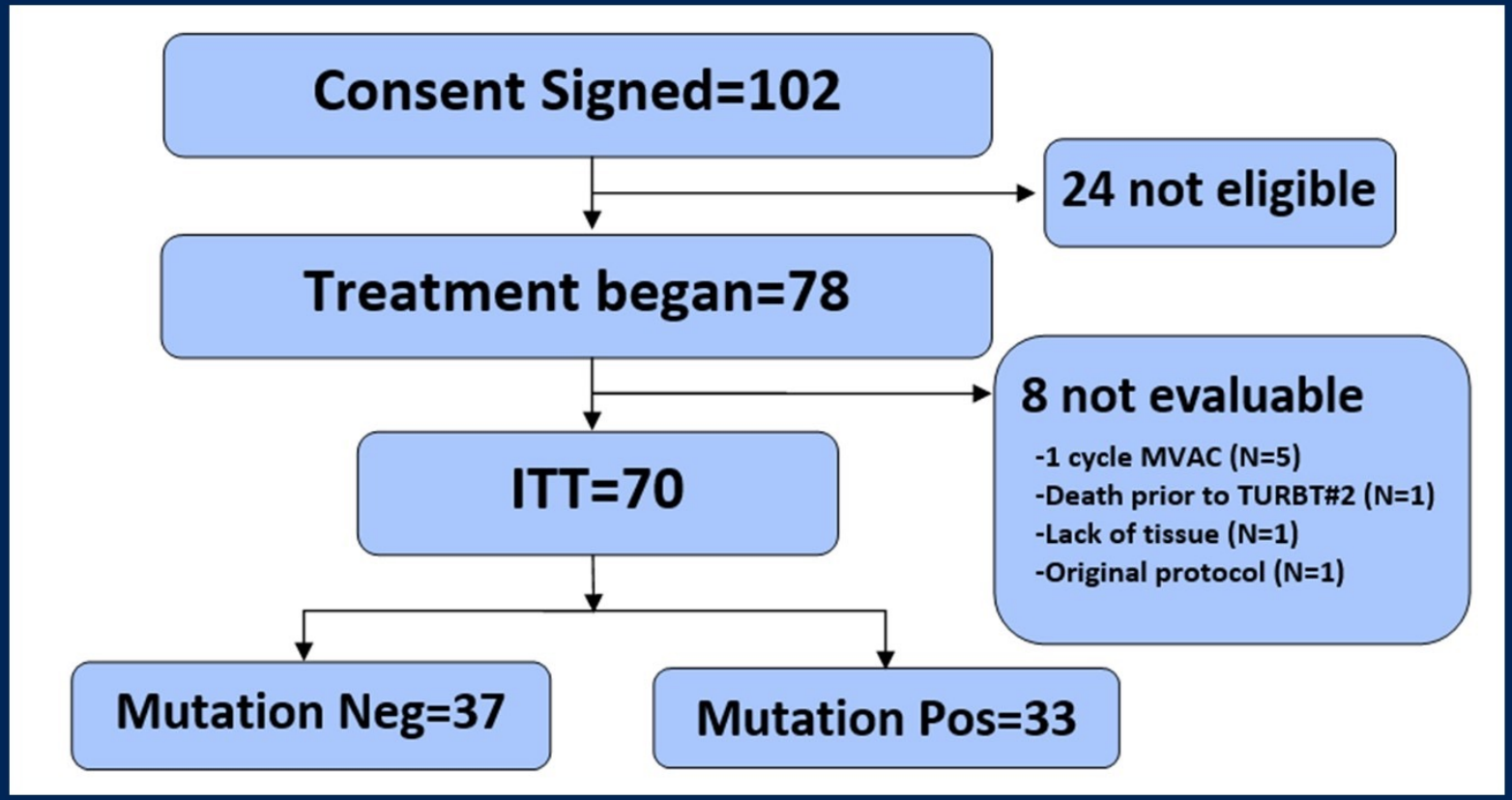

ASCO Genitourinary Cancers Symposium #GU23

PRESENTED BY: Daniel M. Geynisman, MD

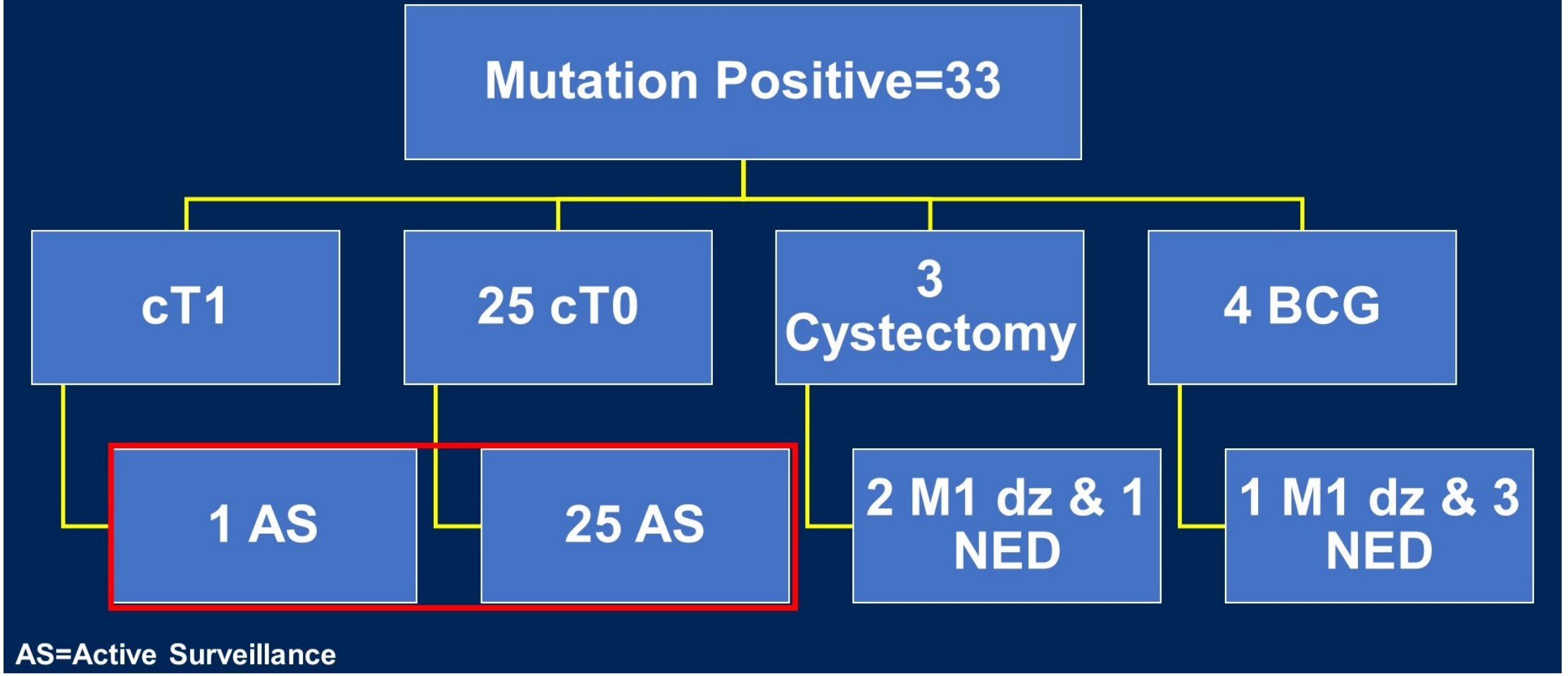


ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

# Results: Over 33 months at 4 academic centers



# Results: Disposition of Mutation Positive Patients

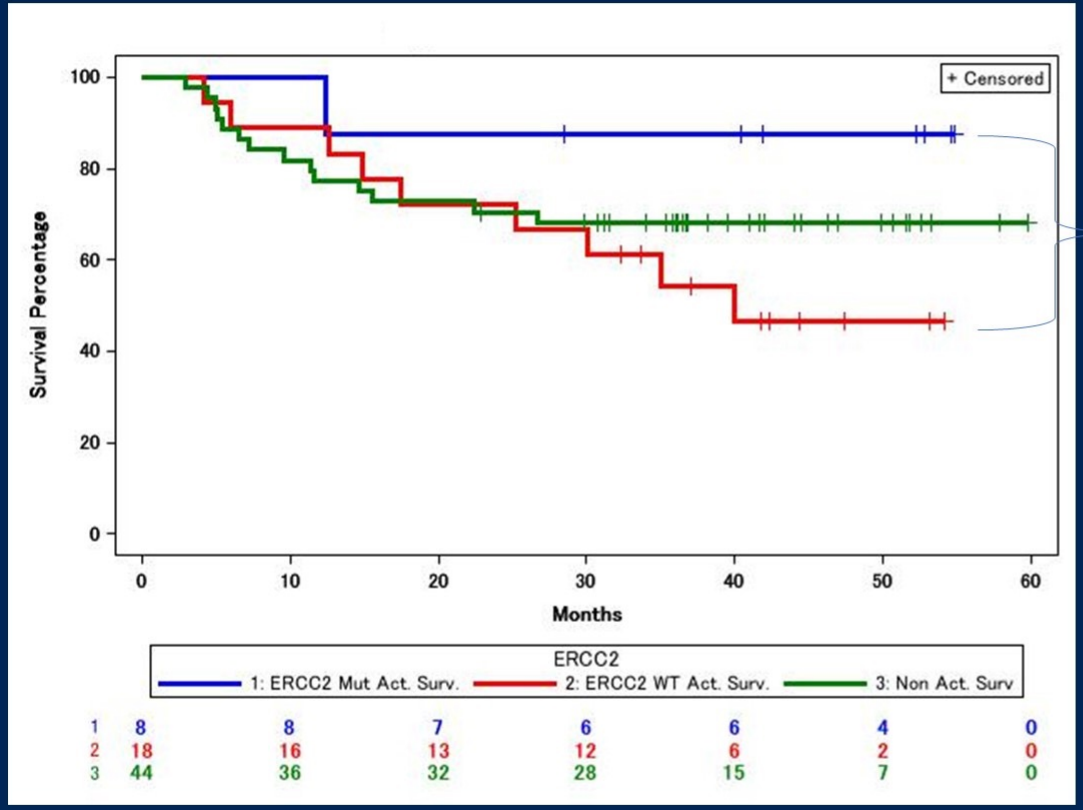





PRESENTED BY: Daniel M. Geynisman, MD

# RETAIN did not meet non-inferiority bounds

## Results: MFS and ERCC2



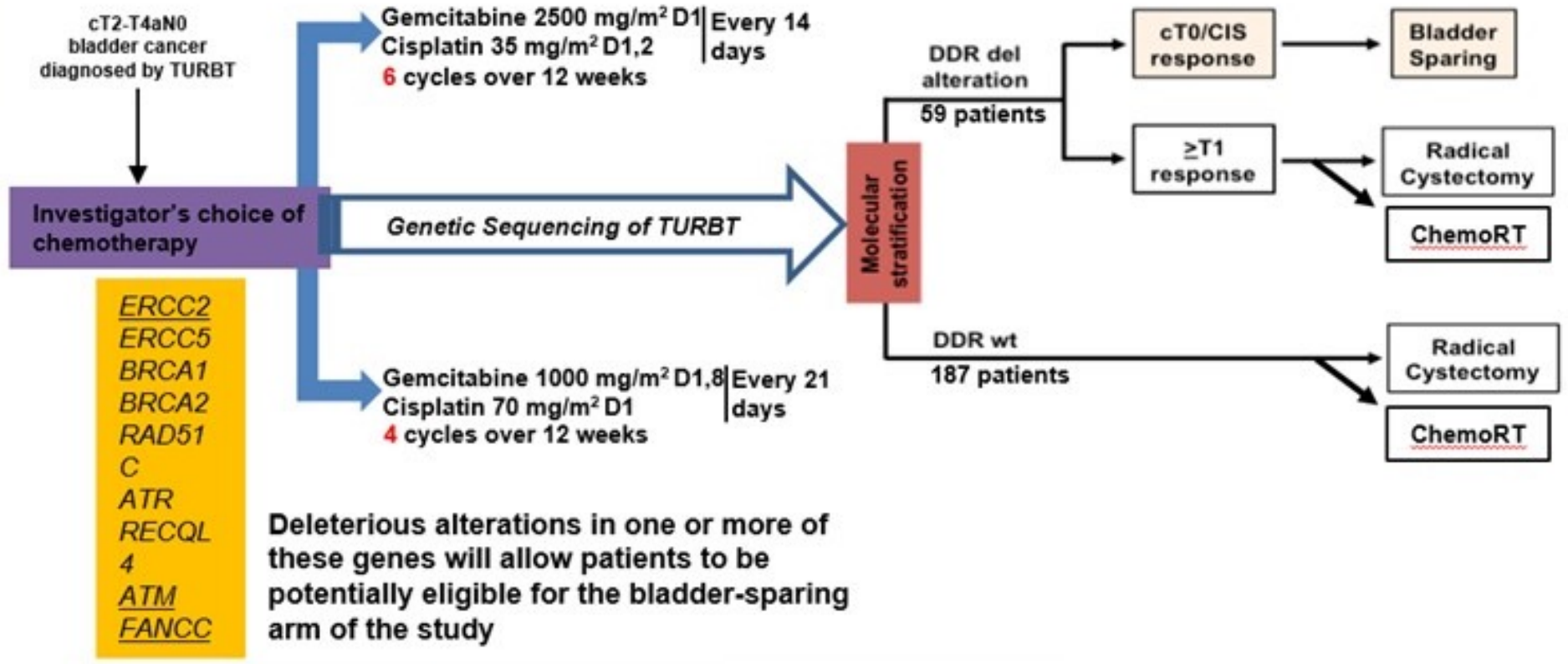

p=0.1

- Associations between mutation presence and MFS or UC recurrence were not observed.



PRESENTED BY: Daniel M. Geynisman, MD

# A031701




PI: G Iyer
NCT03609216

# Future Directions

- DDR mutations may be underappreciated
  - improving screening is important

- Further refinement of DDR mutations as predictive markers

- Downstream targets in development:
  - ATM
  - ATR
  - DNA-PK
  - CHK1
  - WEE1
  - PKMYT1

# Questions?