Integration of PARP Inhibitors into the Management of Metastatic Castration-Resistant Prostate Cancer

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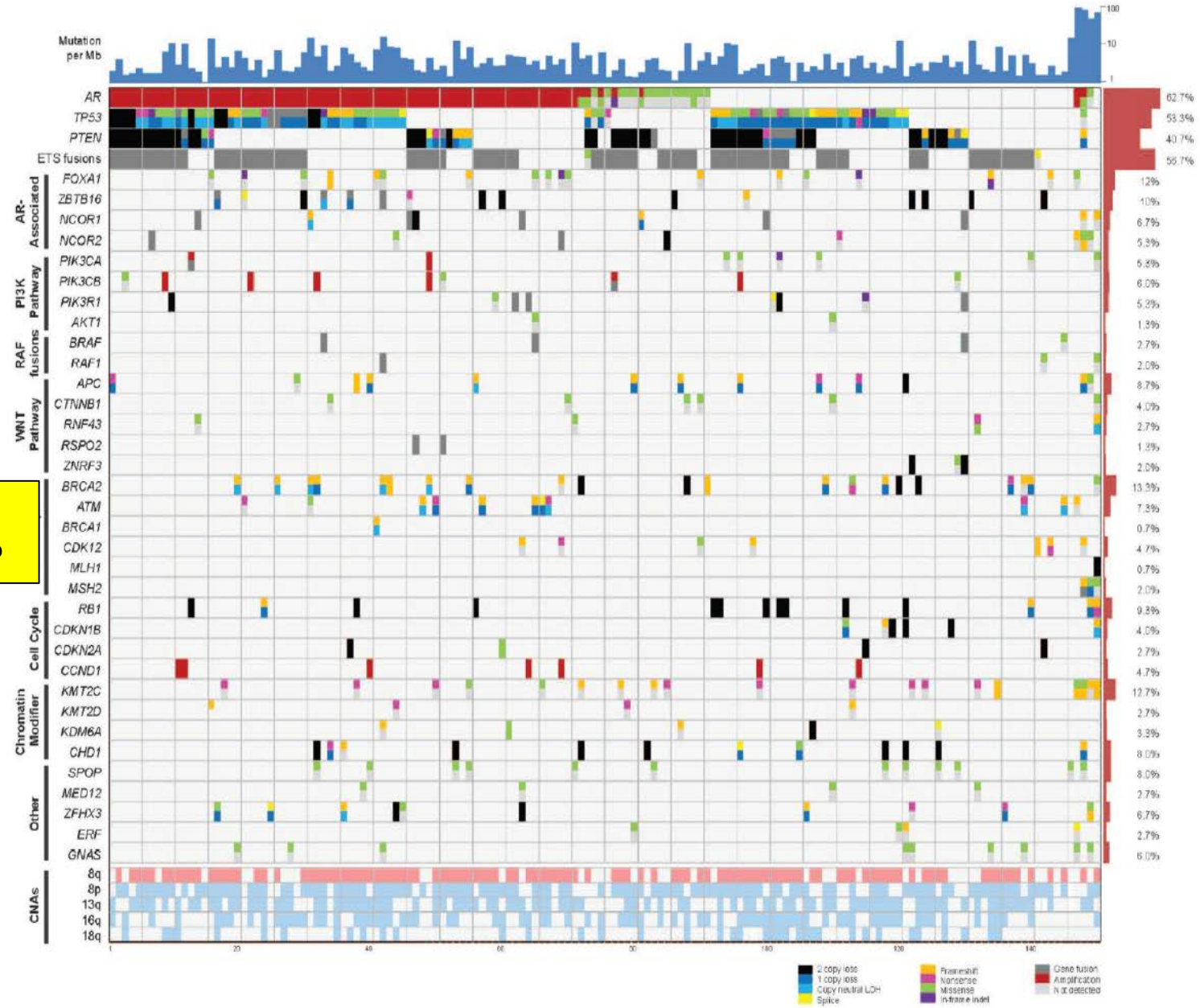
Mutational Landscape of mCRPC

DNA Repair aberrations: 19.3%



Robinson et al (2015) Cell

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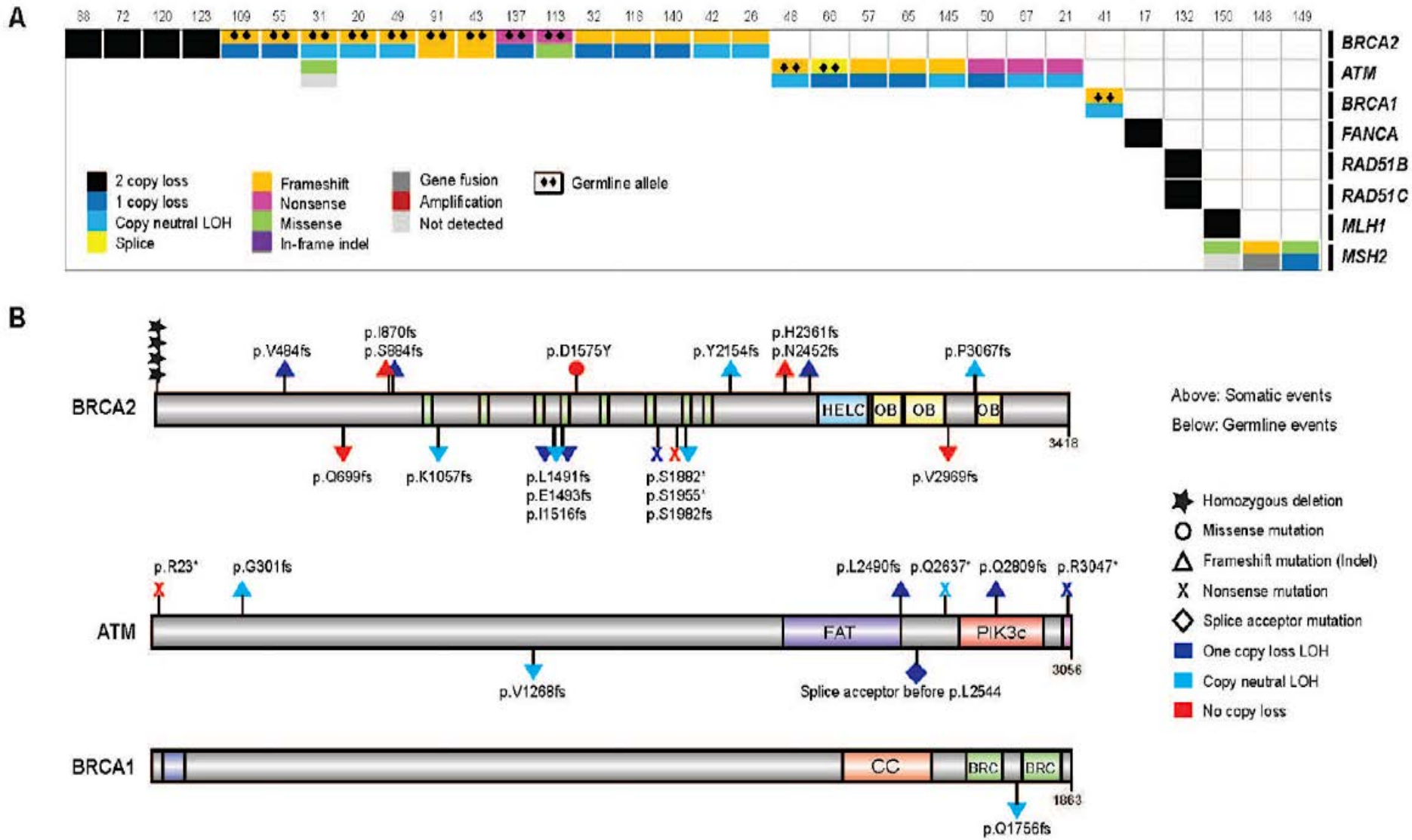
Aberrations in DNA Repair Genes are Common in mCRPC



Robinson et al (2015) Cell

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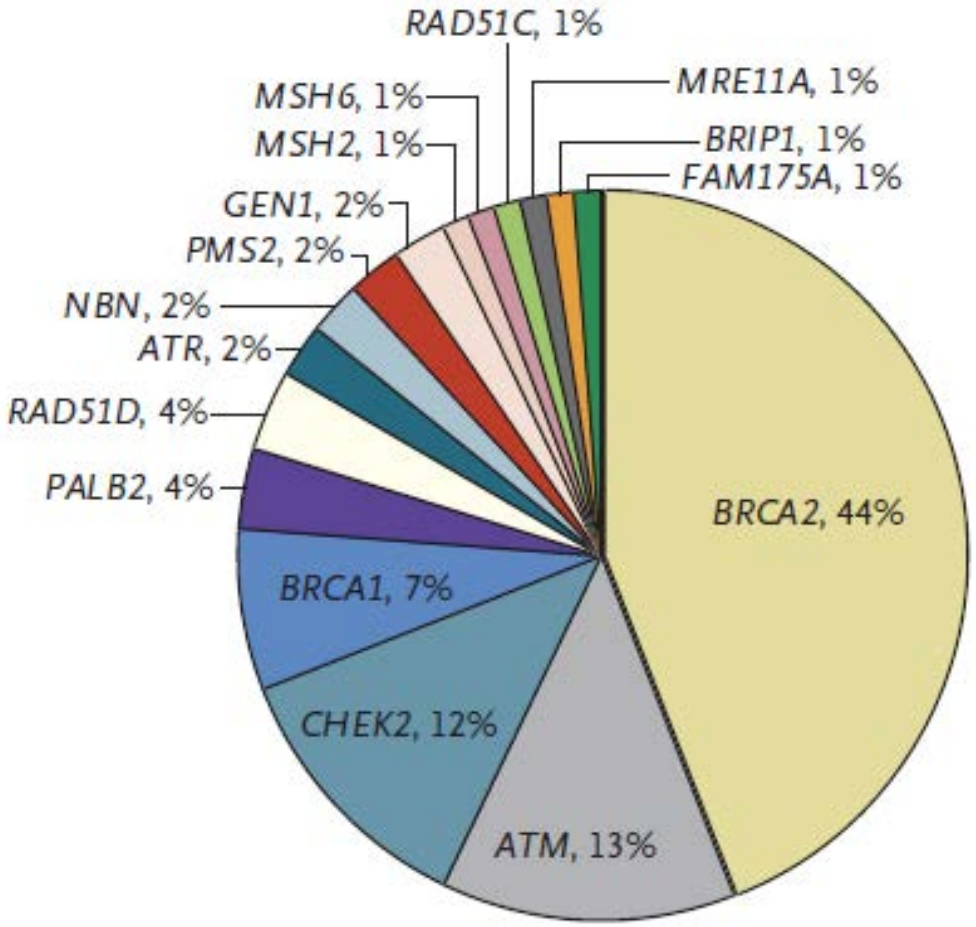
Inherited DNA-Repair Gene Mutations in Men with Metastatic Prostate Cancer

- Multicenter study of 692 men
- Deleterious mutations were found in 82 men (11.8%) in 16 genes
- Observed rate exceeded that associated with localized prostate cancer (4.6%) and general population without cancer (2.7%)



Pritchard et al (2016) NEJM

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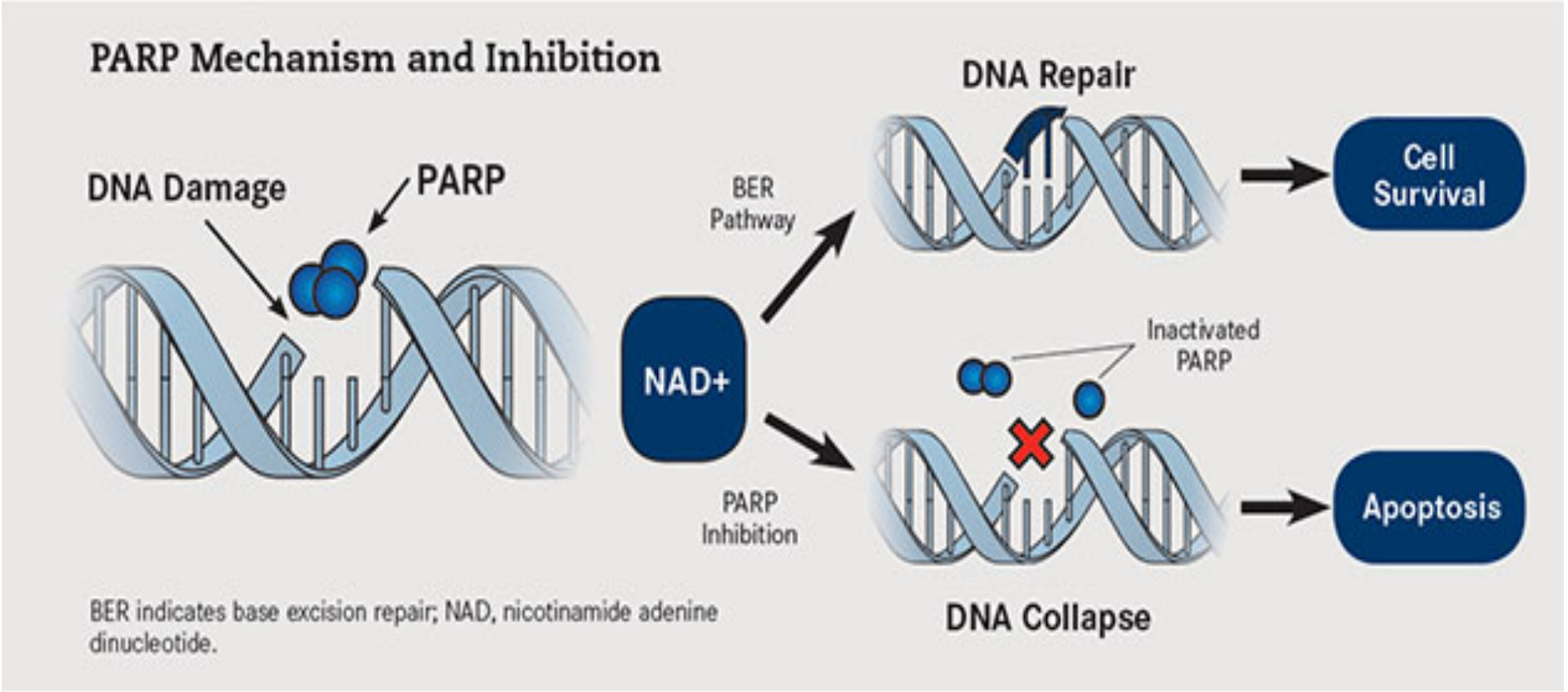
Poly ADP Ribose Polymerase (PARP)



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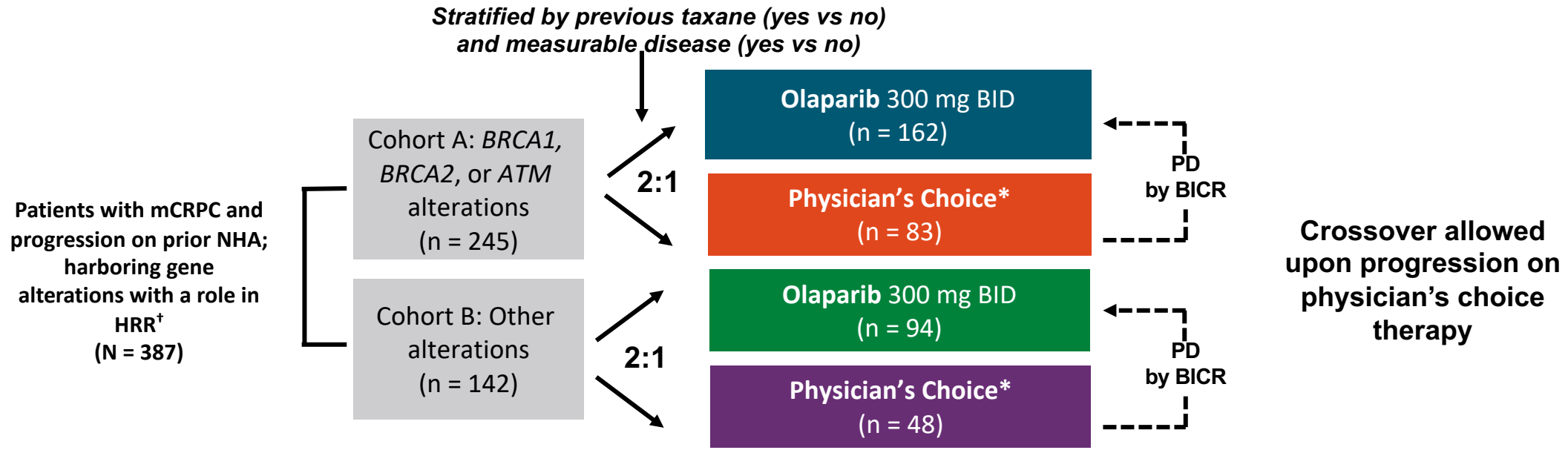
PROfound: Olaparib vs Physician's Choice in mCRPC



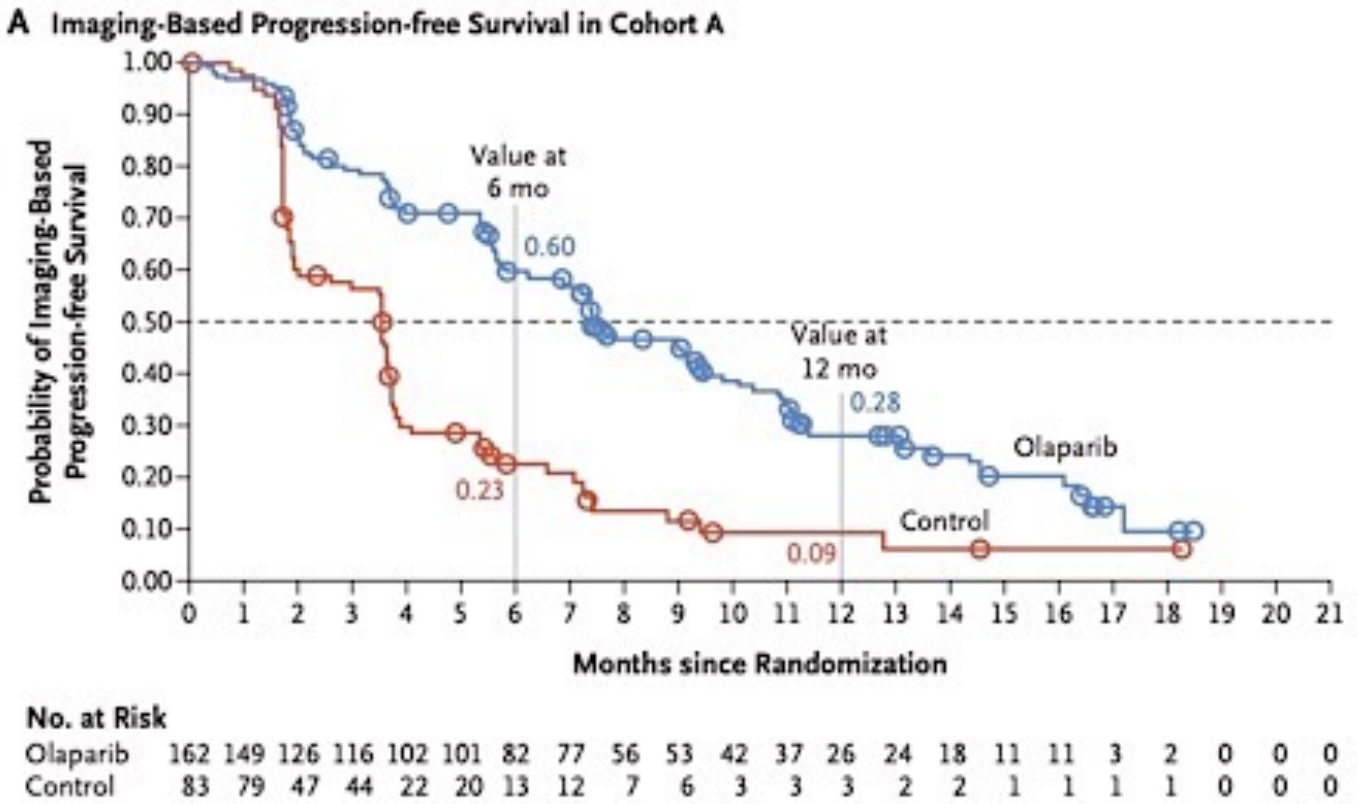
*Enzalutamide 160 mg QD or abiraterone acetate 1000 mg QD plus prednisone 5 mg BID.

†***BRCA1/2, ATM, BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RA51D, or RAD54L.***

- Primary endpoint: radiographic PFS in cohort A by BICR using RECIST 1.1 and PCWG3
- Secondary endpoints: radiographic PFS in both cohorts, confirmed radiographic ORR in cohort A, time to pain progression in cohort A, OS in cohort A

de Bono et al. *N Engl J Med.* 2020;382:2091.

PROfound: Radiographic PFS (Primary Endpoint) - Cohort A



	Median
	mo
Olaparib	7.4
Control	3.6

Hazard ratio for progression or death, 0.34 (95% CI, 0.25–0.47)
P<0.001

de Bono et al. *N Engl J Med.* 2020;382:2091.

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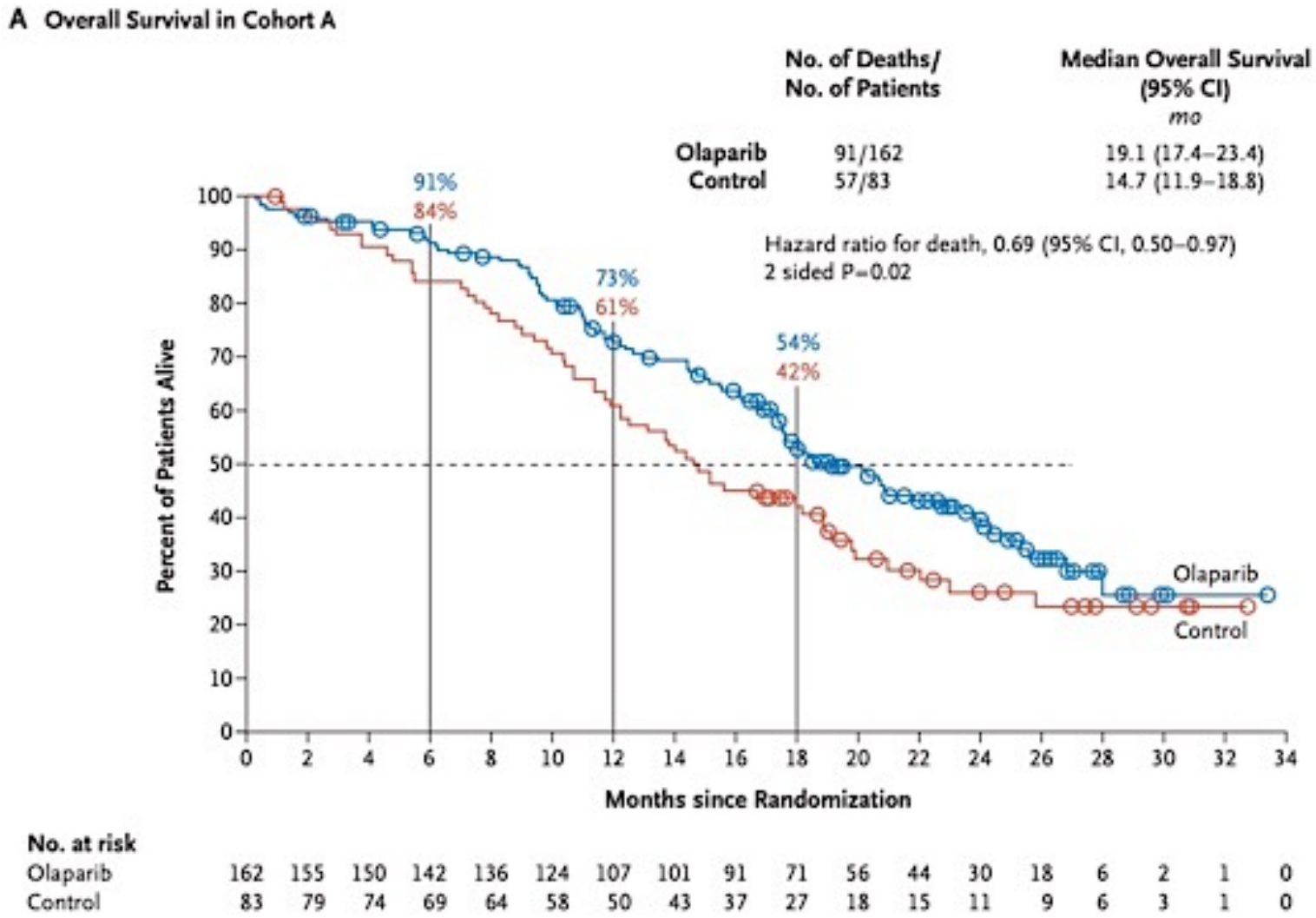
PROfound: Final OS in Cohort A



Hussain et al. *N Engl J Med.* 2020;383(24):2345-57.

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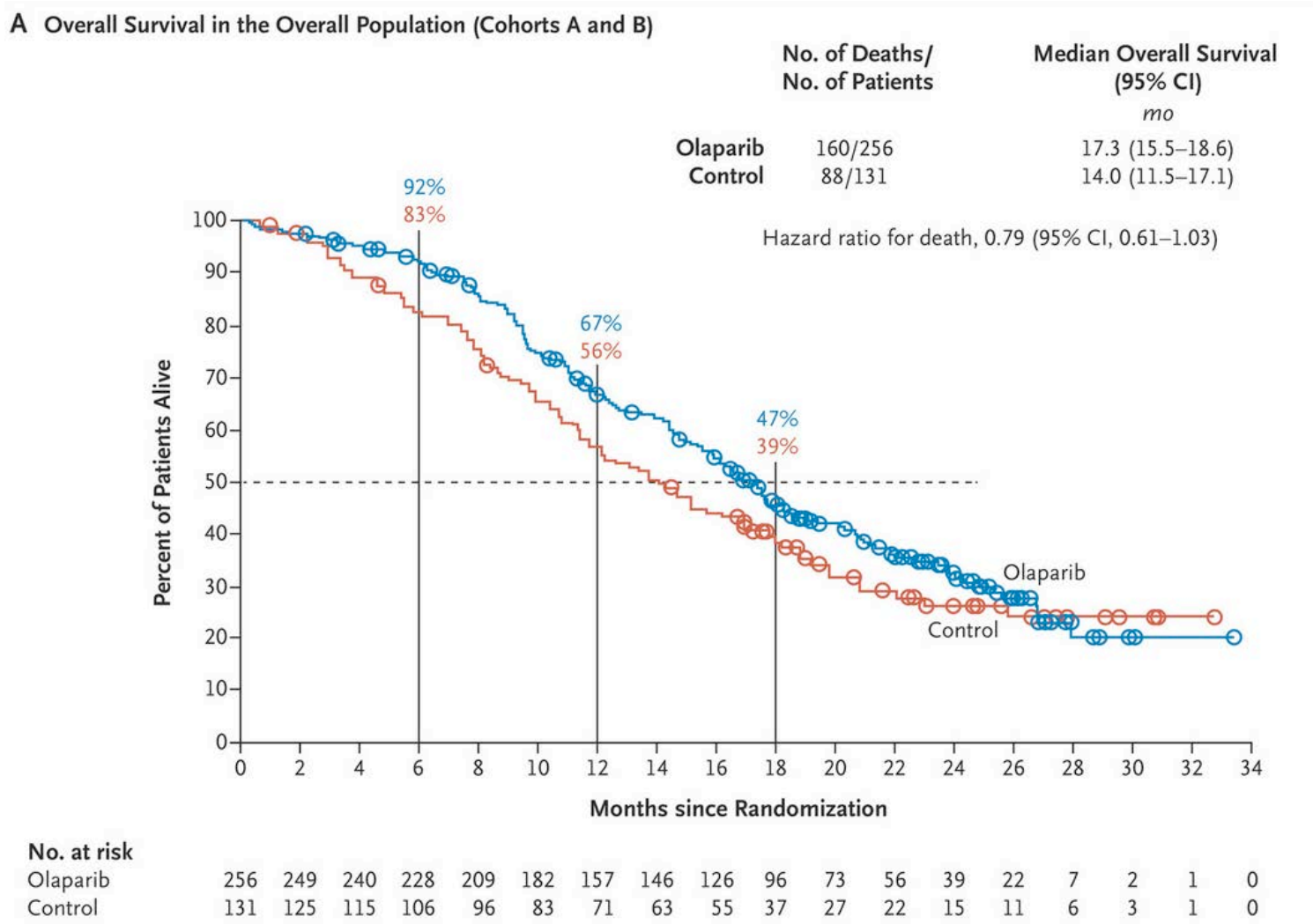
PROfound: OS in Cohort A+B



Hussain et al. *N Engl J Med.* 2020;383(24):2345-57.

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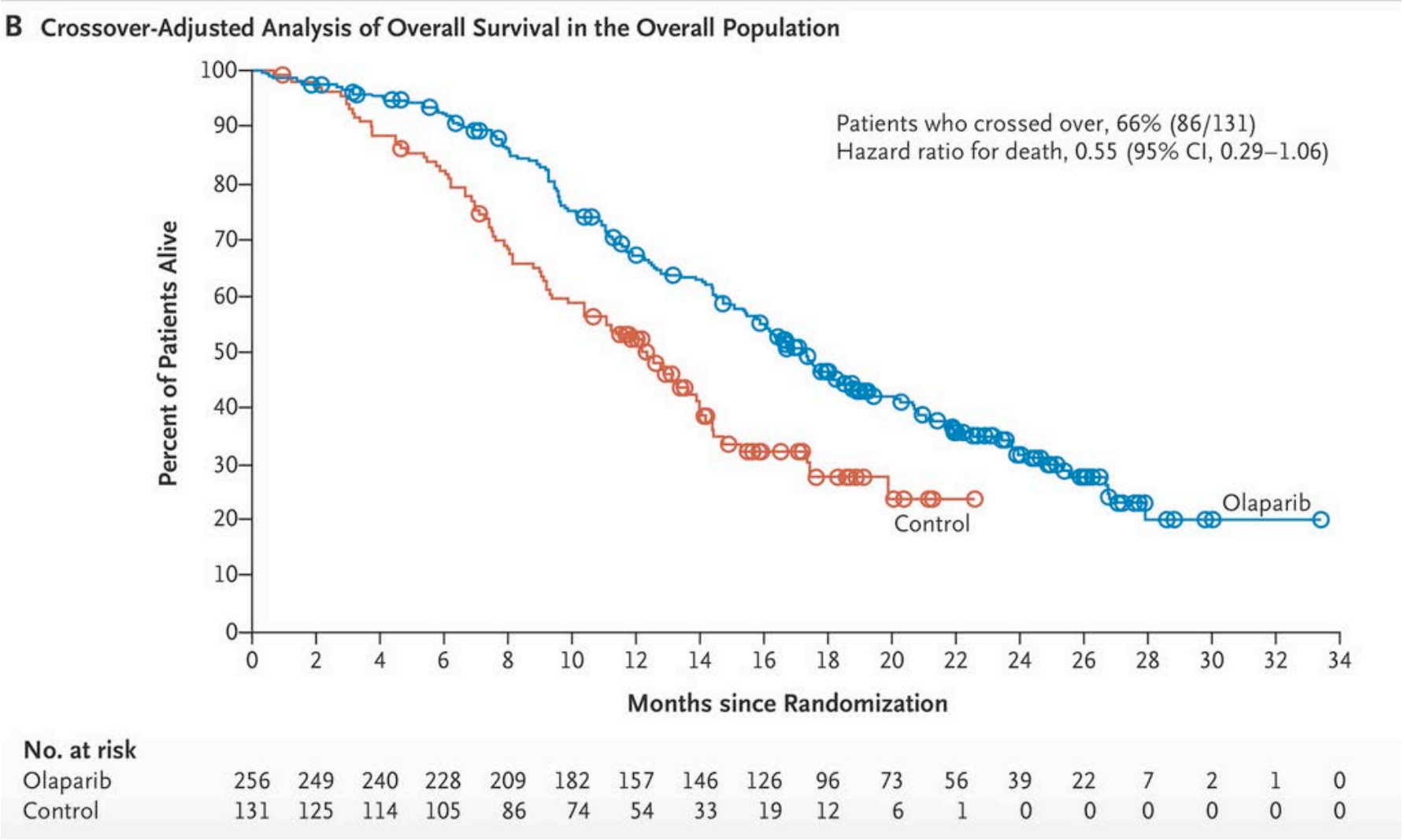
PROfound: Crossover-Adjusted OS in Cohort A+B



Hussain et al. *N Engl J Med.* 2020;383(24):2345-57.

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PROfound: Adverse Event Profile

Table 1. Adverse Events in the Overall Population (Cohorts A and B) and in the Subgroup of Patients Who Crossed Over from Control Therapy to Receive Olaparib.*

Event	Olaparib (N=256)		Control (N=130)†		Crossover (N=83)‡	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients with event (percent)					
Any adverse event	246 (96)	133 (52)	115 (88)	52 (40)	77 (93)	49 (59)
Anemia§	127 (50)	58 (23)	20 (15)	7 (5)	43 (52)	24 (29)
Nausea	110 (43)	4 (2)	27 (21)	0	24 (29)	2 (2)
Fatigue or asthenia¶	107 (42)	8 (3)	43 (33)	7 (5)	21 (25)	8 (10)
Decreased appetite	80 (31)	4 (2)	24 (18)	1 (<1)	15 (18)	2 (2)
Diarrhea	55 (21)	2 (<1)	9 (7)	0	12 (14)	0
Vomiting	51 (20)	6 (2)	17 (13)	1 (<1)	16 (19)	1 (1)
Constipation	49 (19)	0	19 (15)	0	12 (14)	0
Back pain	36 (14)	2 (<1)	18 (14)	2 (2)	8 (10)	0
Peripheral edema	34 (13)	0	10 (8)	0	3 (4)	0
Cough	29 (11)	0	3 (2)	0	4 (5)	0
Dyspnea	27 (11)	6 (2)	5 (4)	0	4 (5)	1 (1)
Arthralgia	26 (10)	1 (<1)	14 (11)	0	4 (5)	0
Urinary tract infection	21 (8)	5 (2)	15 (12)	5 (4)	12 (14)	3 (4)
Any serious adverse event‖	94 (37)	NA	39 (30)	NA	27 (33)	NA
Interruption of treatment because of adverse event	119 (46)	NA	25 (19)	NA	44 (53)	NA
Dose reduction because of adverse event	60 (23)	NA	7 (5)	NA	27 (33)	NA
Discontinuation of treatment due to adverse event	51 (20)	NA	11 (8)	NA	11 (13)	NA
Death due to adverse event	10 (4)	NA	6 (5)	NA	3 (4)	NA

Hussain et al. *N Engl J Med.* 2020 [Epub].

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PROfound: Safety Summary

Median treatment duration: Olaparib 7.4 months; Physician's choice 3.9 months

	Olaparib (N=256)	Physician's choice (N=130)
Any AE, n (%)	244 (95.3)	114 (87.7)
Any AE of CTCAE grade 3 or higher, n (%)	130 (50.8)	49 (37.7)
Dose reduction due to AE, n (%)	57 (22.3)	5 (3.8)
Discontinuation due to AE, n (%)	42 (16.4)	11 (8.5)
Death due to AE, n (%)	10 (3.9)	5 (3.8)
Reported to be related to study treatment	1 (0.4)	1 (0.8)

AEs are reported irrespective of attribution, unless otherwise stated

Hussain M, et al. 2019 ESMO. Abstract LBA12.

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TRITON2: Rucaparib in Metastatic CRPC With HRR Gene Alterations

- International, multicenter, open-label phase II study

Patients with mCRPC and deleterious somatic or germline alteration in HRR genes*; progression on AR-directed tx† for PC and 1 prior line of taxane-based CT for CRPC; no prior PARPi, mitoxantrone, cyclophosphamide, or platinum-based CT; ECOG PS 0/1
(N = 190‡)

Rucaparib 600 mg BID in 28-d cycles §

Until radiographic progression or discontinuation for other reason

*Local or central testing of blood or tumor samples for alterations in HRR genes: ***BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK2, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D, RAD54L***. †Abiraterone, enzalutamide, or apalutamide. ‡Enrollment cutoff: February 28, 2019.
§ Assessments: tumor Q8W for 24 wks, then Q12W; PSA Q4W.

- Primary endpoints
  - *Among patients with measurable disease at BL:* centrally assessed, confirmed ORR per modified RECIST¶/PCWG3
  - *Among patients without measurable disease at BL:* locally assessed, confirmed PSA response (≥50% decrease) rate

¶RECIST modified to include up to 10 target lesions (maximum 5 per site), excluding prostatic bed or bone lesions; MRI permitted.

Abida et al. ESMO 2018. Abstract 793PD; Abida et al. *J Clin Oncol* 2020;38(32):3763-72.

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TRITON2: ORR in *BRCA1*/*BRCA2* Cohort

TABLE 2. Rate of Response to Rucaparib Treatment

Response	Investigator-Evaluable Population (n = 65)	IRR-Evaluable Population (n = 62)
Confirmed ORR, No. (%; 95% CI)[a]	33 (50.8; 38.1 to 63.4)	27 (43.5; 31.0 to 56.7)
Complete response	4 (6.2)	7 (11.3)
Partial response	29 (44.6)	20 (32.3)
Stable disease	25 (38.5)	28 (45.2)
Progressive disease	6 (9.2)	6 (9.7)
Not evaluable	1 (1.5)	1 (1.6)

	Overall Efficacy Population (n = 115)
Confirmed PSA response rate, No. (5; 95% CI)	63 (54.8; 45.2 to 64.1)

NOTE. Data presented as No. (%) unless otherwise indicated. Visit cutoff date: December 23, 2019.
Abbreviations: IRR, independent radiology review; ORR, objective response rate; PSA, prostate-specific antigen.
[a]Per modified RECIST/Prostate Cancer Clinical Trials Working Group 3 criteria.

Abida et al. *J Clin Oncol* 2020;38(32):3763-72.

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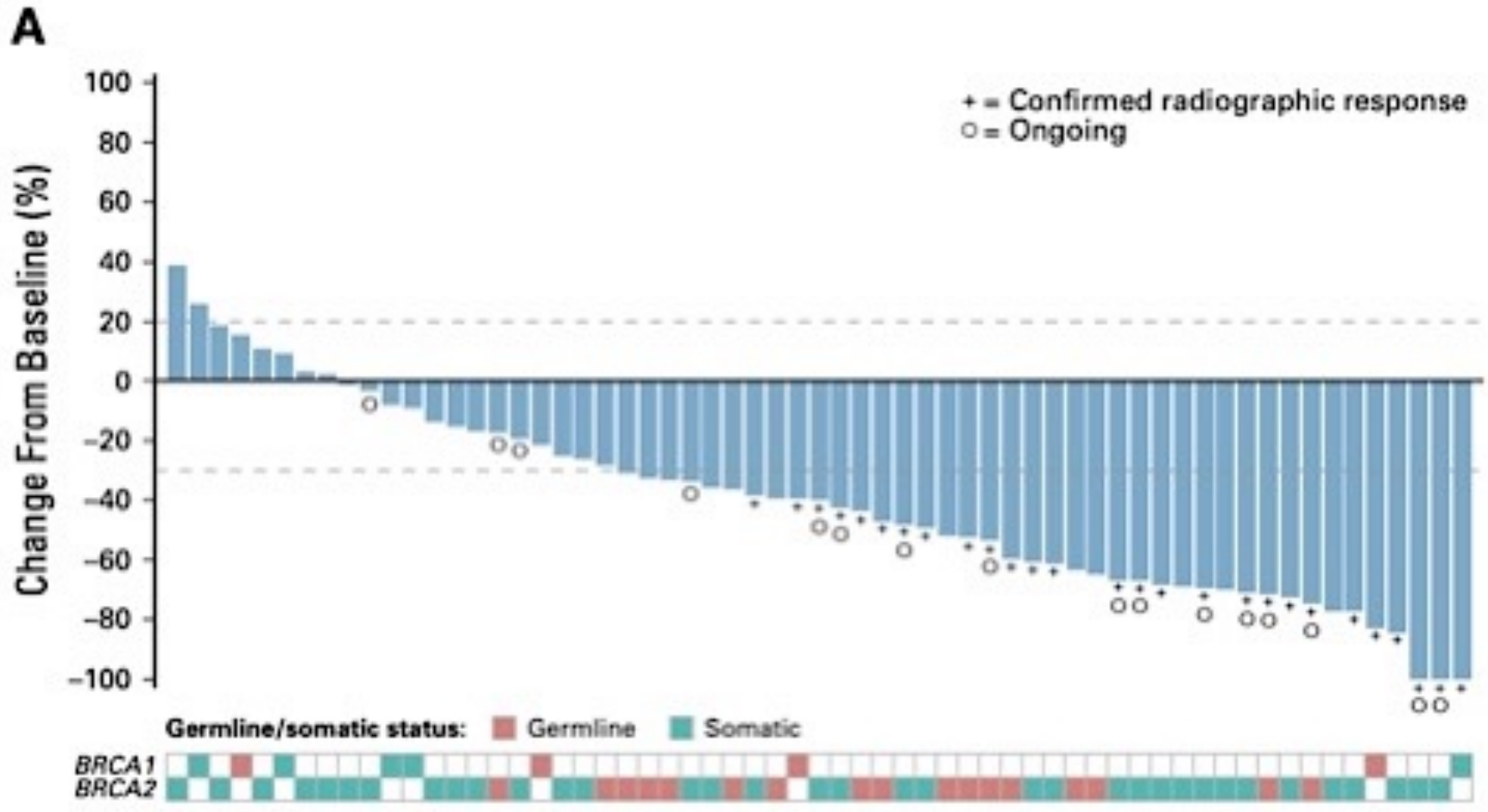
TRITON2: Tumor Response in *BRCA1*/*BRCA2* Cohort



Abida et al. *J Clin Oncol* 2020;38(32):3763-72.

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TRITON2: Adverse Event Profile

TABLE 3. Most Commonly Reported TEAEs (N = 115)

Individual TEAE (preferred terms) Occurring in ≥ 15% of Patients	Any Grade	Grade ≥ 3
Asthenia/fatigue	71 (61.7)	10 (8.7)
Nausea	60 (52.2)	3 (2.6)
Anemia/decreased hemoglobin	50 (43.5)	29 (25.2)
ALT/AST increased	38 (33.0)	6 (5.2)
Decreased appetite	32 (27.8)	2 (1.7)
Constipation	31 (27.0)	1 (0.9)
Thrombocytopenia/decreased platelets	29 (25.2)	11 (9.6)
Vomiting	25 (21.7)	1 (0.9)
Diarrhea	23 (20.0)	0
Dizziness	21 (18.3)	0
Blood creatinine increased	18 (15.7)	1 (0.9)

NOTE. Data presented as No. (%). Visit cutoff date: September 13, 2019. TEAEs were graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03. There were no TEAEs of myelodysplastic syndrome or acute myeloid leukemia reported.

Abbreviation: TEAE, treatment-emergent adverse event.

Abida et al. *J Clin Oncol* 2020;38(32):3763-72.

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[aaa,bbb,ccc]

FIRST-LINE TREATMENT

- Preferred regimens:
  - Abiraterone[t] (category 1[ddd])
  - Docetaxel[yy,eee] (category 1)
  - Enzalutamide[t] (category 1)
  - Sipuleucel-T[yy,fff] (category 1)
- Useful in certain circumstances:
  - Radium-223[ggg] for symptomatic bone metastases (category 1)
  - Mitoxantrone for palliation in symptomatic patients with visceral metastases who cannot tolerate other therapies[yy]
- Other recommended regimens
  - Fine-particle abiraterone[t]
  - Other secondary hormone therapy[t]

SECOND-LINE TREATMENT

First-line abiraterone/enzalutamide[hhh,iii]

- Preferred regimens:
  - Docetaxel (category 1)[yy,ccc]
  - Sipuleucel-T[yy,fff]
- Useful in certain circumstances:
  - Olaparib for HRRm (category 1)[kkk]
  - Pembrolizumab for MSI-H or dMMR[yy] (category 2B)
  - Radium-223[ggg] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCAm[lll]
- Other recommended regimens:
  - Abiraterone[t]
  - Cabazitaxel[yy]
  - Enzalutamide[t]
  - Fine-particle abiraterone[t]
  - Other secondary hormone therapy[t]

First-line docetaxel[iii]

- Preferred regimens:
  - Abiraterone[t] (category 1)
  - Cabazitaxel[yy] (category 1)[jjj]
  - Enzalutamide[t] (category 1)
- Useful in certain circumstances:
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy]
  - Olaparib for HRRm (category 2B)[kkk]
  - Pembrolizumab for MSI-H or dMMR[yy] (category 2B)
  - Radium-223[ggg] for symptomatic bone metastases (category 1)
  - Rucaparib for BRCAm[lll]
- Other recommended regimens:
  - Consider docetaxel rechallenge[yy,ccc]
  - Fine-particle abiraterone[t]
  - Sipuleucel-T[yy,fff]
  - Other secondary hormone therapy[t]

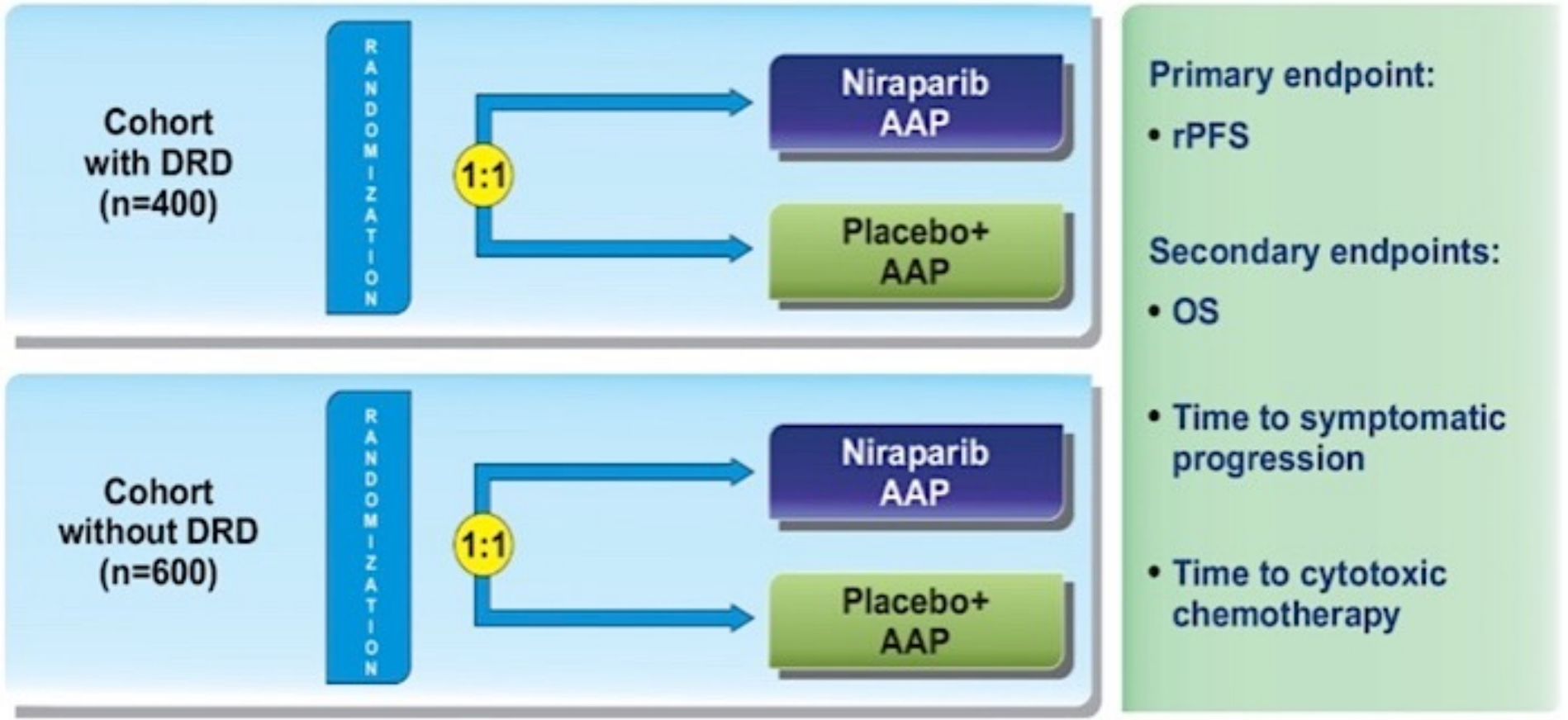
SUBSEQUENT TREATMENT

(All systemic therapies are category 2B if visceral metastases are present)

- Preferred regimens:
  - Abiraterone[t] (category 1[ddd])
  - Cabazitaxel[yy] (category 1[ddd])
  - Docetaxel rechallenge[yy,ccc]
  - Enzalutamide[t] (category 1[ddd])
- Useful in certain circumstances:
  - Olaparib for HRRm (category 1)[kkk]
  - Pembrolizumab for MSI-H or dMMR[yy] (category 2B)
  - Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[yy]
  - Radium-223[ggg] for symptomatic bone metastases (category 1[ddd])
  - Rucaparib for BRCAm[lll]
- Other recommended regimens:
  - Fine-particle abiraterone[t]
  - Other secondary hormone therapy[t]

See footnotes (PROS-16A).

MAGNITUDE: Phase 3 Study of Abiraterone +/- Niraparib



ClinicalTrials.gov Identifier: NCT03748641

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Conclusions

- DNA repair gene alterations are common in metastatic prostate cancer
- Both germline and somatic testing are recommended
- PARP inhibitors have demonstrated efficacy in mCRPC
- Olaparib and rucaparib are FDA approved in mCRPC
- Ongoing clinical trials are testing PARP inhibitors in combination with other agents

CASES

Case 1

- 2008 NCCN intermediate-risk prostate cancer at age 45
- 11/2008 prostatectomy; pT3bN0 Gleason 4+5
  Post-operative PSA nadir <0.1
- 11/2009 PSA 0.54; treated with salvage radiation therapy
- 2010-started continuous ADT for PSA recurrence
- 2012 PSA 7.2; restaging with metastases to pelvic and retroperitoneal nodes
- 3/2012-2/2015: abiraterone acetate plus prednisone
  PSA nadir <0.1; discontinued for disease progression
- 10/2016-6/2017: docetaxel. Best response was partial response; discontinued for disease progression
- 11/2017 PSA 110. Restaging demonstrated progression in pelvic and retroperitoneal nodes

Case 1 (continued)

- Family History
  - Father died from prostate cancer at age 62
  - Brother with NCCN high risk prostate at age 57
- Germline genetic testing reported pathogenic BRCA2 mutation c5350_5351delAA (p.Asn1784HIsfsX2)
- 11/2017-12/2018 Olaparib
  - PSA declined from 181 to nadir of 34
  - Treatment was accompanied by nausea and altered taste
  - Discontinued for disease progression; restaging with new liver metastases

Case 2

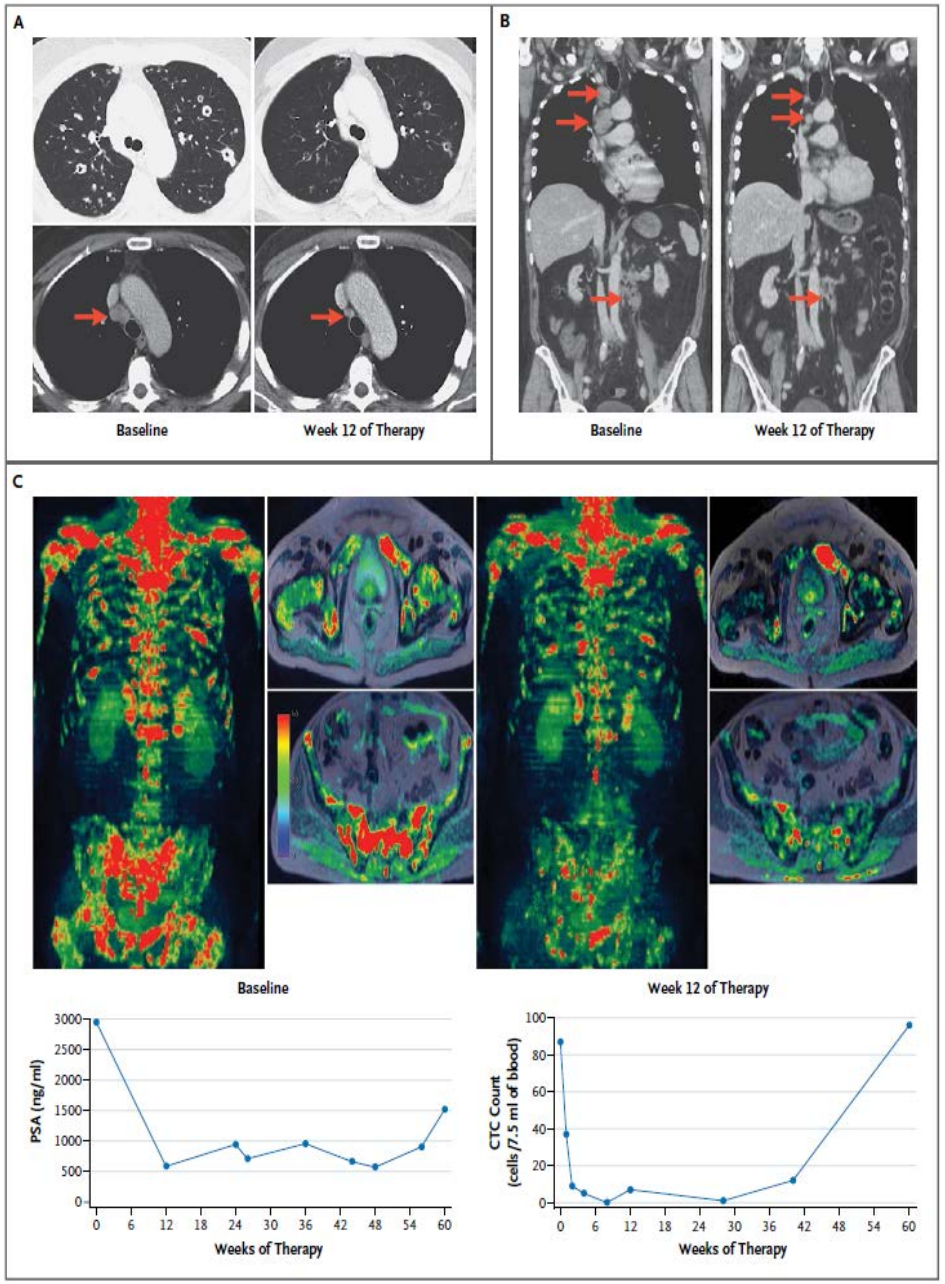
- In 2015, patient was diagnosed with prostate cancer at age 57 after presenting with back pain and anemia
- PSA >1,000, MRI with extensive bone metastases
- 10/2015 started continuous ADT
- 11/2015-3/2016 docetaxel x 6 cycles of mHSPC
- 11/2016 radiation to skull base after presenting with diplopia
- 2/2017-6/2017 retreated with docetaxel; discontinued for progression
- 8/2017-4/2018 abiraterone acetate plus prednisone; best response was progressive disease.
- 4/2018 PSA 290. Restaging with extensive bone metastases

Case 2 (continued)

- Family History
  - Father died from prostate cancer at age 91
  - Mother died from breast cancer at age 61
- Germline genetic testing with pathogenic BRCA2 mutation c.3847_3848delGT (p.Val1283Lysfs*2)
- 4/2018-1/2019 Olaparib
  - He had treatment interruptions and dose reductions for hematologic toxicity (low ANC, anemia)
  - Prompt improvement in pain
  - PSA declined from 290 to nadir of 90
  - Discontinued for clinical disease progression

BACKUP SLIDES

DNA-Repair Defects and Olaparib in mCRPC



Mateo et al (2016) NEJM

DNA-Repair Defects and Olaparib in mCRPC

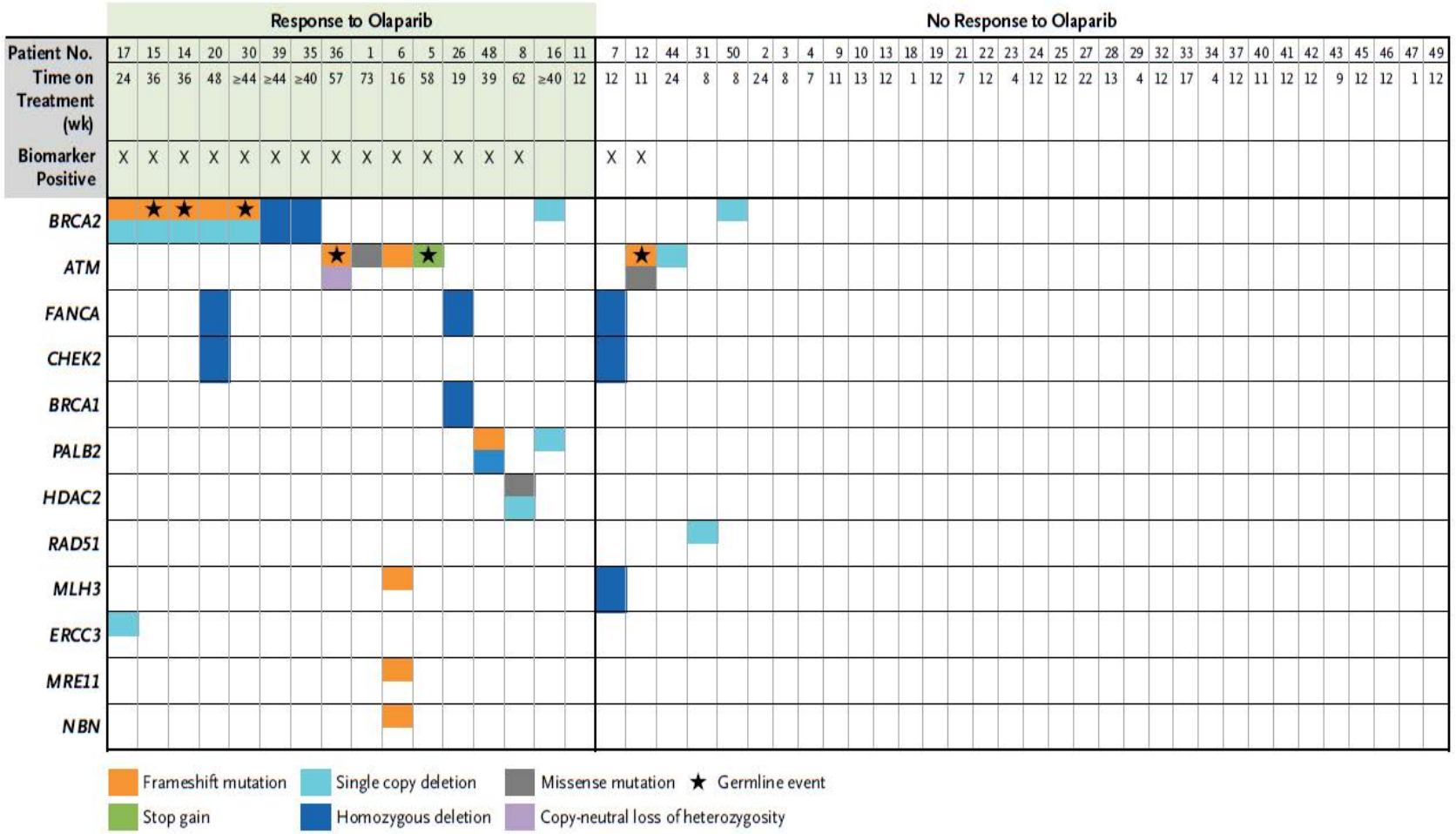
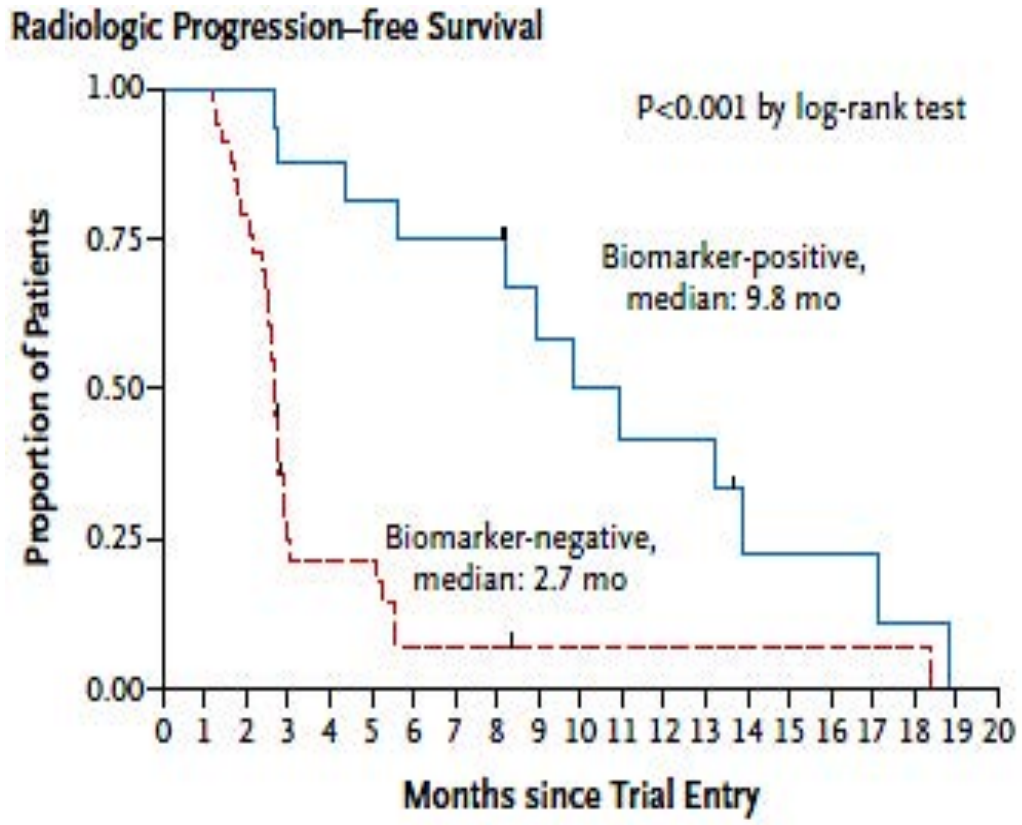


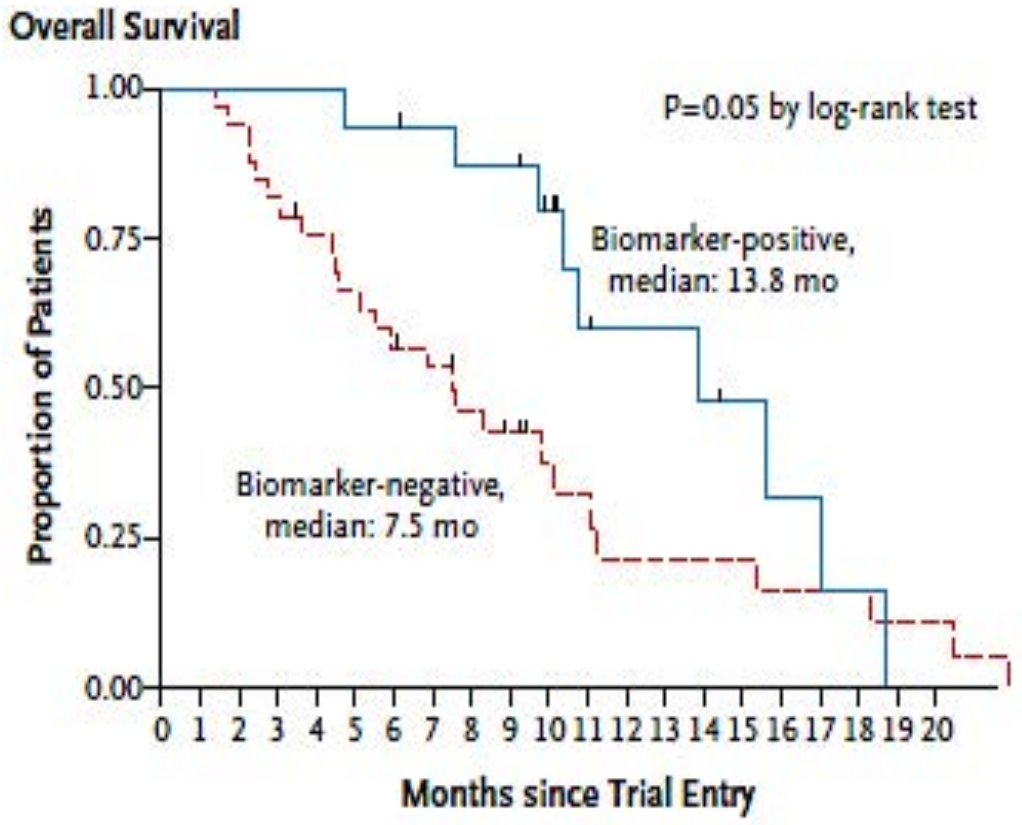
Figure 1. Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.

Data are shown for the 49 patients who could be evaluated for a response. Mutations and deletions in DNA-repair genes were identified through next-generation sequencing studies. Green shading indicates patients who were classified as having a response to olaparib in the clinical trial. Patients were considered to be biomarker-positive if homozygous deletions, deleterious mutations, or both were detected in DNA-repair genes (but not single copy deletions without events detected in the second allele). A star indicates that a particular genomic event was detected in germline DNA. Archival tumor samples were used for the sequencing studies in Patients 13, 18, 21, 40, 41, and 49 because the biopsy samples obtained during the trial were negative for tumor content.

Mateo et al (2016) NEJM

DNA-Repair Defects and Olaparib in mCRPC





Mateo et al (2016) NEJM

PROPEL: Phase 3 Study of Abiraterone +/- Olaparib

ClinicalTrials.gov Identifier: NCT03732820

TRITON2: Safety Summary

Median Treatment Duration

- Overall safety population, 3.7 mo (range, 0.5-12.9)
- Patients with a *BRCA1/2* alteration, 4.4 mo (range, 0.50-12.0)

Table 4. Summary of TEAEs

Table 4. Summary of TEAEs

	Overall safety population (N=85), n (%)
At least 1 TEAE	81 (95.3%)
At least 1 TEAE grade ≥3	45 (52.9%)
Treatment interruption and/or dose reduction due to TEAE	45 (52.9%)
Treatment interruption due to TEAE	41 (48.2%)
Dose reduction due to TEAE	25 (29.4%)[a]
TEAE leading to discontinuation	5 (5.9%)[b]
Death due to TEAE	1 (1.2%)[c]

TRITON2: Safety Summary

Table 5. Most Common (≥10%) TEAEs of Any Grade in All Patients Regardless of Causality

	Overall safety population (N=85)	
	Any grade, n (%)	Grade ≥3, n (%)
Asthenia/fatigue	38 (44.7%)	4 (4.7%)
Nausea	36 (42.4%)	3 (3.5%)
Anaemia/decreased haemoglobin	24 (28.2%)	13 (15.3%)
Decreased appetite	24 (28.2%)	3 (3.5%)
Constipation	19 (22.4%)	1 (1.2%)
ALT/AST increased	18 (21.2%)	4 (4.7%)
Vomiting	17 (20.0%)	0
Diarrhoea	16 (18.8%)	1 (1.2%)
Arthralgia	11 (12.9%)	1 (1.2%)
Dizziness	11 (12.9%)	0
Back pain	10 (11.8%)	2 (2.4%)
Oedema peripheral	10 (11.8%)	0
Weight decreased	10 (11.8%)	0
Dysgeusia	9 (10.6%)	0
Dyspnoea	9 (10.6%)	0
Haematuria	9 (10.6%)	3 (3.5%)

Visit cutoff date: 29 June 2018.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

Aims

- Describe the recent evidence for PARPi for patients with mCRPC and homologous recombination repair (HRR)

- Discuss the emerging role of PARPi in prostate cancer
  - Optimal selection based on germline and tumor genetic testing
  - Potential role of PARPi in combination with other agents
  - Potential role of PARPi in other disease states

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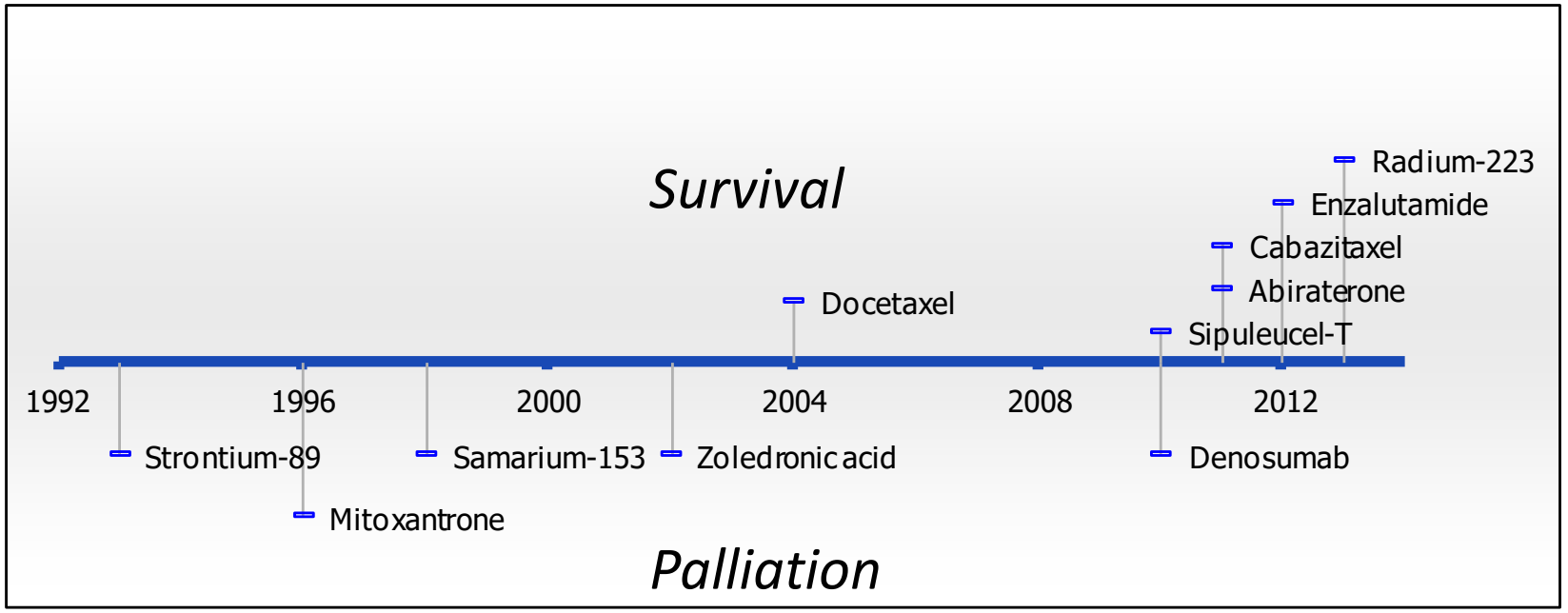
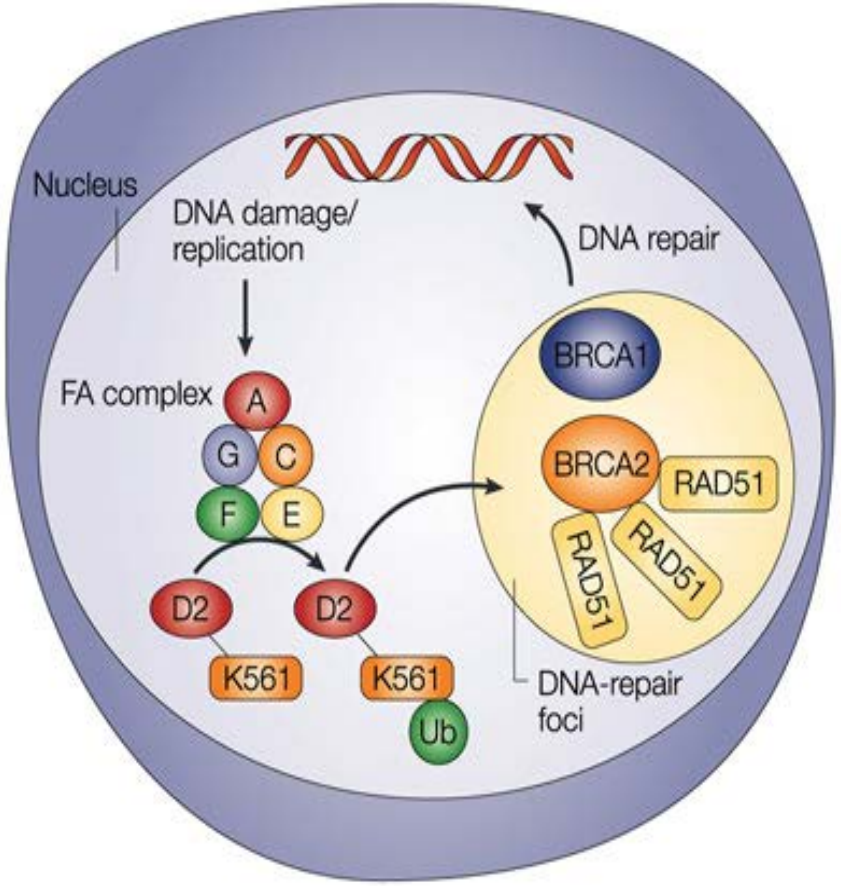
Timeline of FDA Approvals in Metastatic Castration-Resistant Prostate Cancer (mCRPC)



BRCA1 and BRCA2 Pathway



Nature Reviews | Cancer

BRCA1/BRCA2mutations:

- Missing protein
- Nonfunctional protein

Leads to defective:

- DNA repair
- Transcription
- Cell cycle checkpoint regulation

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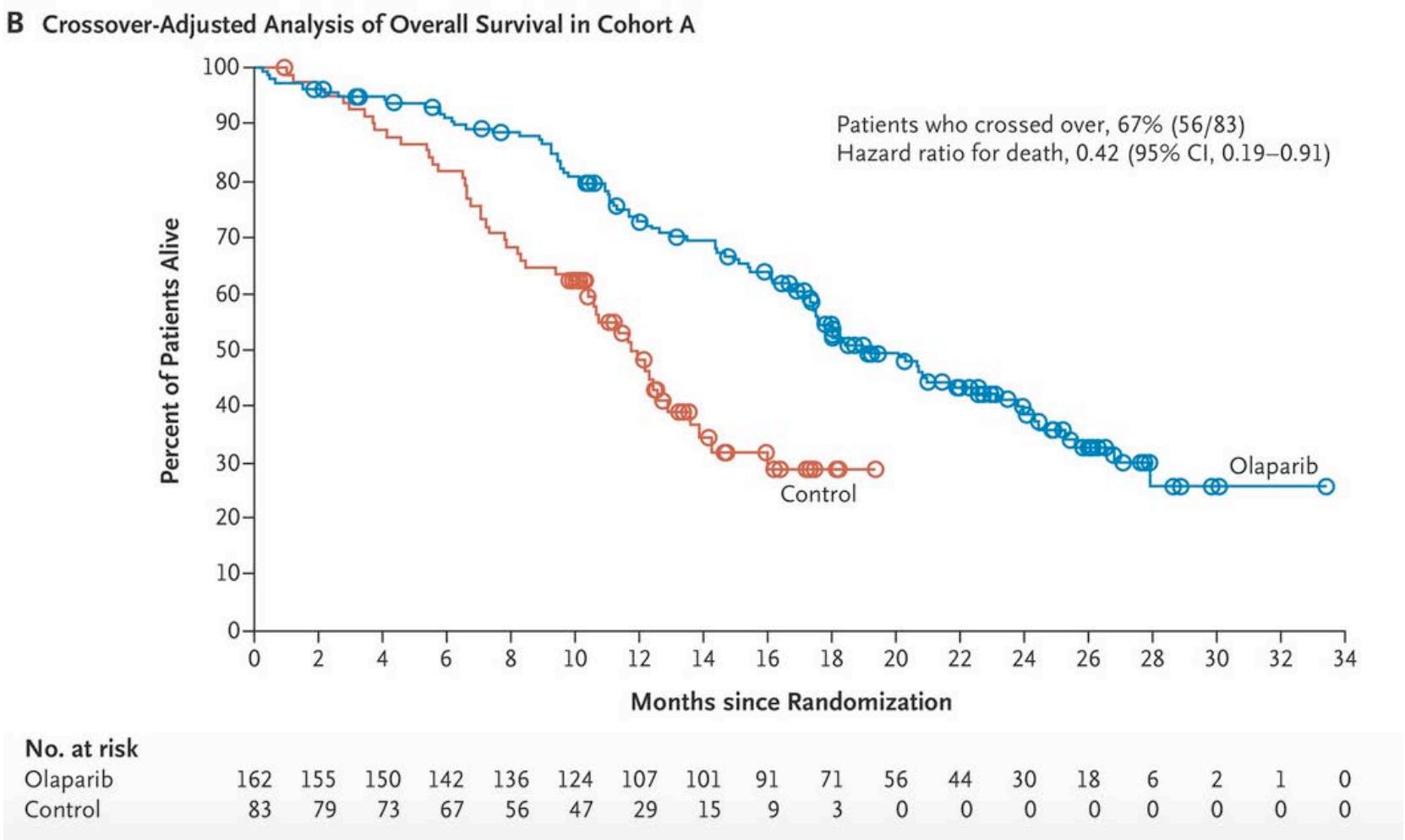
CANCER CENTER

PROfound: Final Crossover-Adjusted OS in Cohort A



Hussain et al. *N Engl J Med.* 2020 [Epub].