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How Precision Medicine and Novel Prostate Cancer Treatments Can Benefit You

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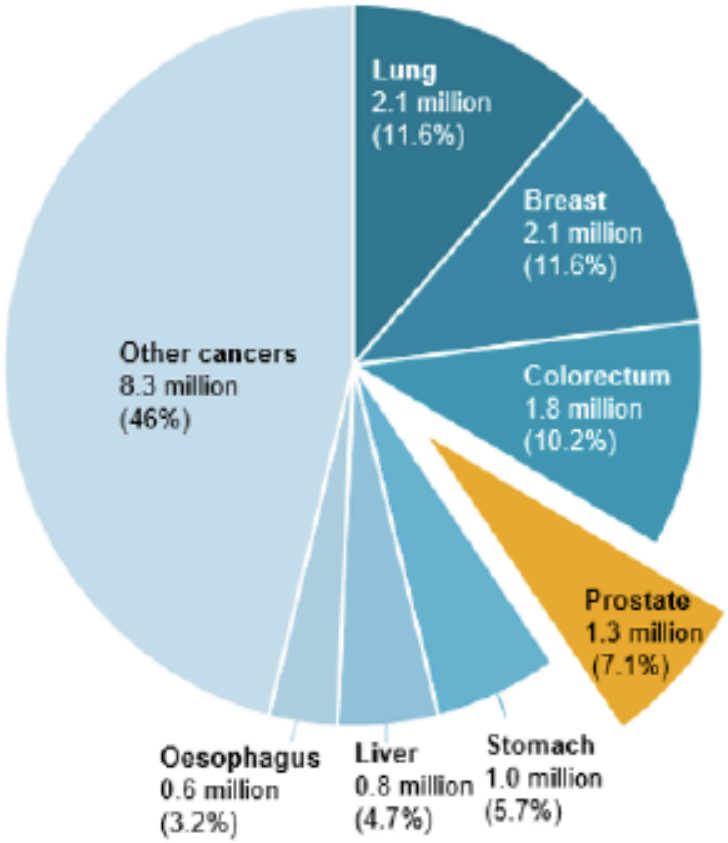
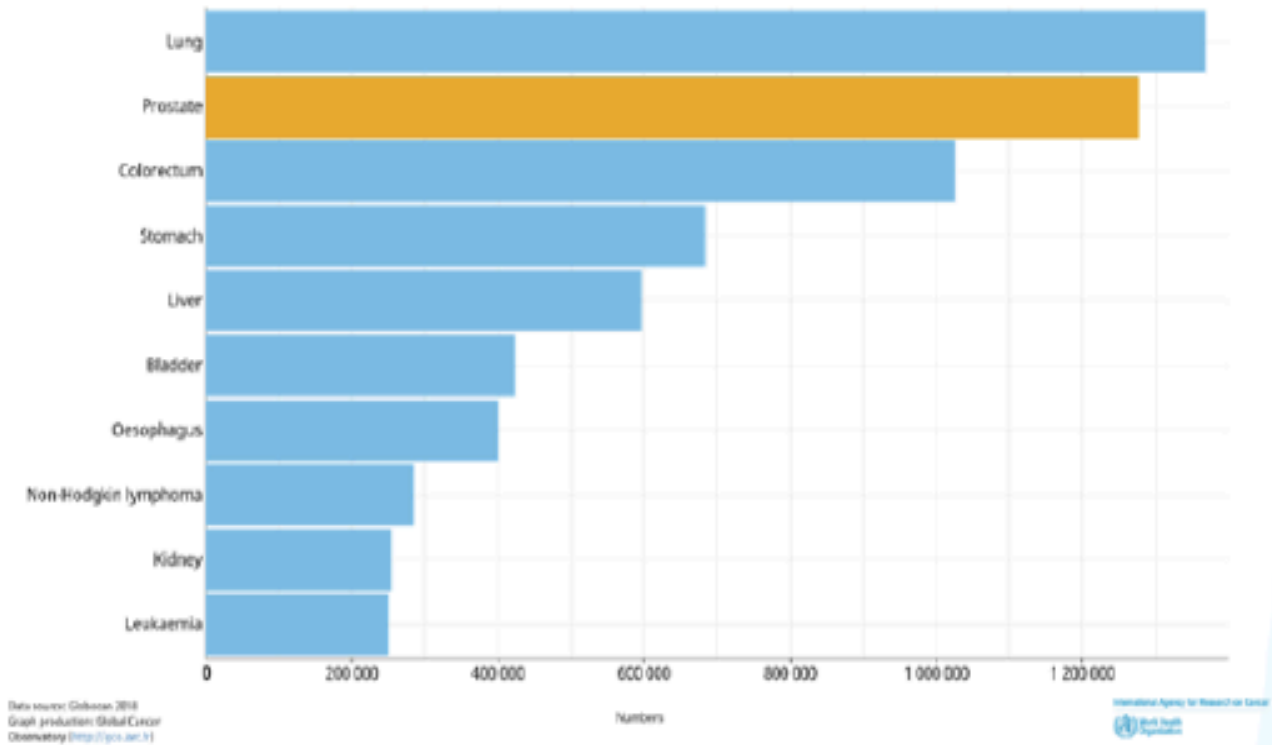
Prostate cancer is ranked as the fourth most frequently diagnosed cancer worldwide*[1]

There are over 1.3 million new cases per year, making it the second most frequently diagnosed cancer in men[1,2]

Estimated number of new cases in 2018, worldwide, all cancers, both sexes, all ages[1]



Estimated incidence of worldwide cancer cases in males of all ages, in 2018[2]



*Both sexes, all ages

1. Bray F et al. *CA Cancer J Clin.* 2018;68:394-424; 2. GLOBOCAN 2018 statistics. http://gco.iarc.fr (accessed May 2019)

Prostate Cancer

- Globally, prostate cancer is the second most common form of malignancy in men[1]
- Across the world, prostate cancer is the 4th most common form of cancer-related death in men[1]
- Globally, a million and a quarter men were diagnosed with prostate cancer in 2018. That's almost 3500 men per day, 146 per hour, or more than 2 a minute![2]
- If this is a 50 minute talk, that's more than 100 new diagnoses

1. Bray F, et al. CA Cancer J Clin 2018;68:394–424;
2. Rawla P *World J Oncol* 2019;10:63–89.

How Precision Medicine and Novel Prostate Cancer Treatments Can Benefit You

- Precision Medicine: Profound trial, Hopkins Trial
- Novel hormonal Rx: PROSPER, SPARTAN, ARAMIS
- AR Degraders: Arvinas Trial
- Immunotherapy Trials: Merck and Magic 8
- NEPC
- Prostate Cancer Disparities: AA P-1000 and DoD

Personalized Cancer Medicine

- Prevention in BRCA1 & BRCA2 population
- “My chances of developing breast cancer have dropped from 87 percent to under 5 percent”.
- “I can tell my children that they don’t need to fear they will lose me to breast cancer”.

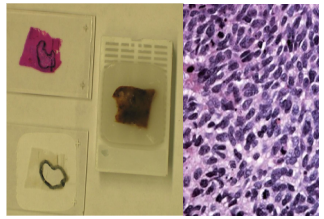
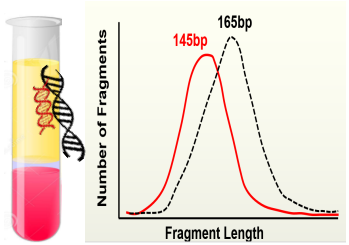
The ANGELINA Effect

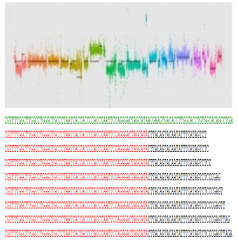
Photo by Gade Skidmore

http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html?_r=0. Accessed 3/31/17.

Emerging Model For Advanced Prostate Cancer

Germline, tumor, liquid biopsy evaluated



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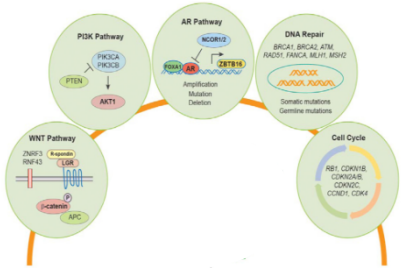
Therapy guided by germline and somatic findings

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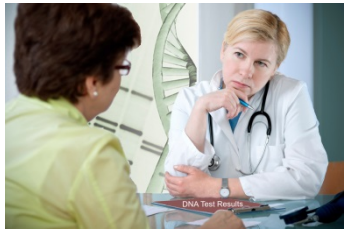
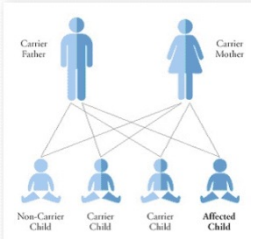
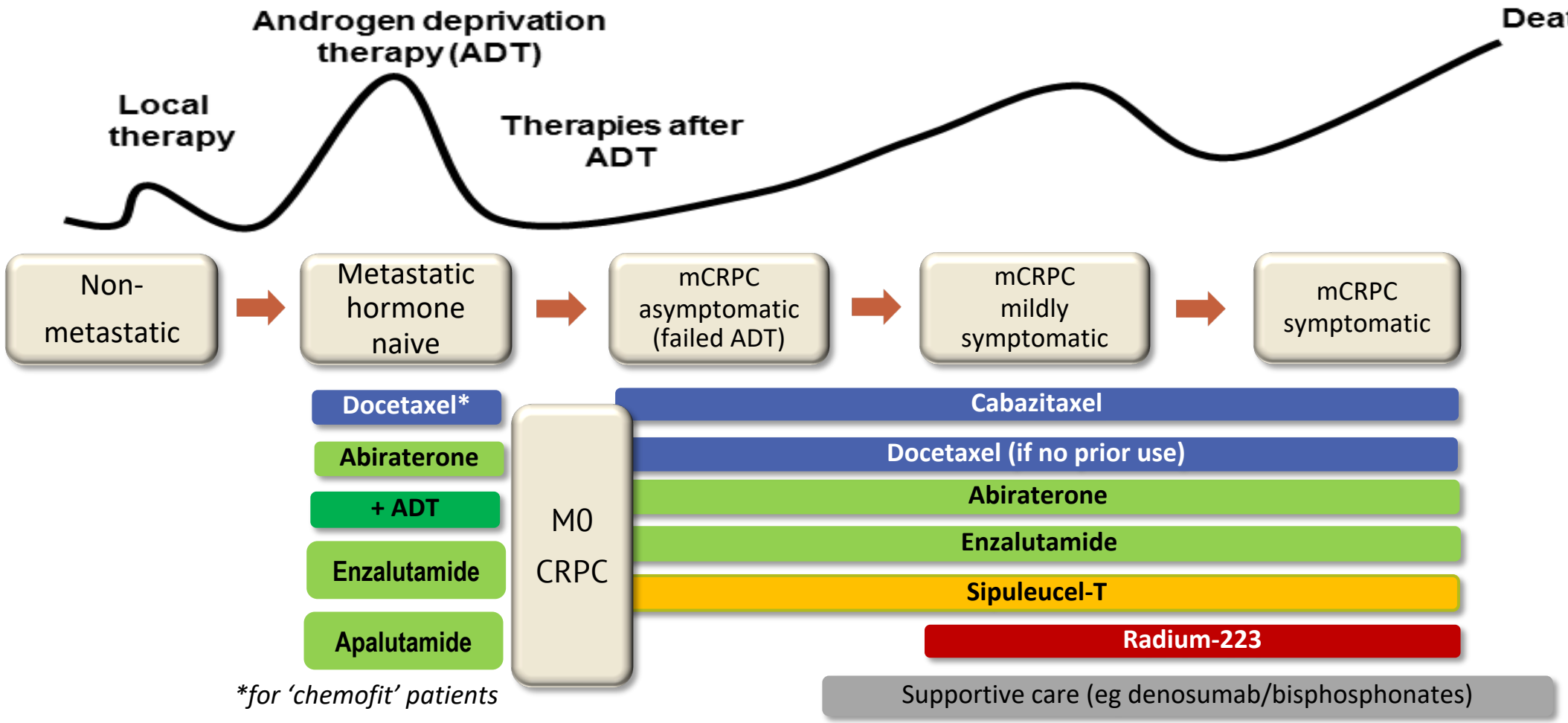
Genetic counseling based on somatic and germline findings



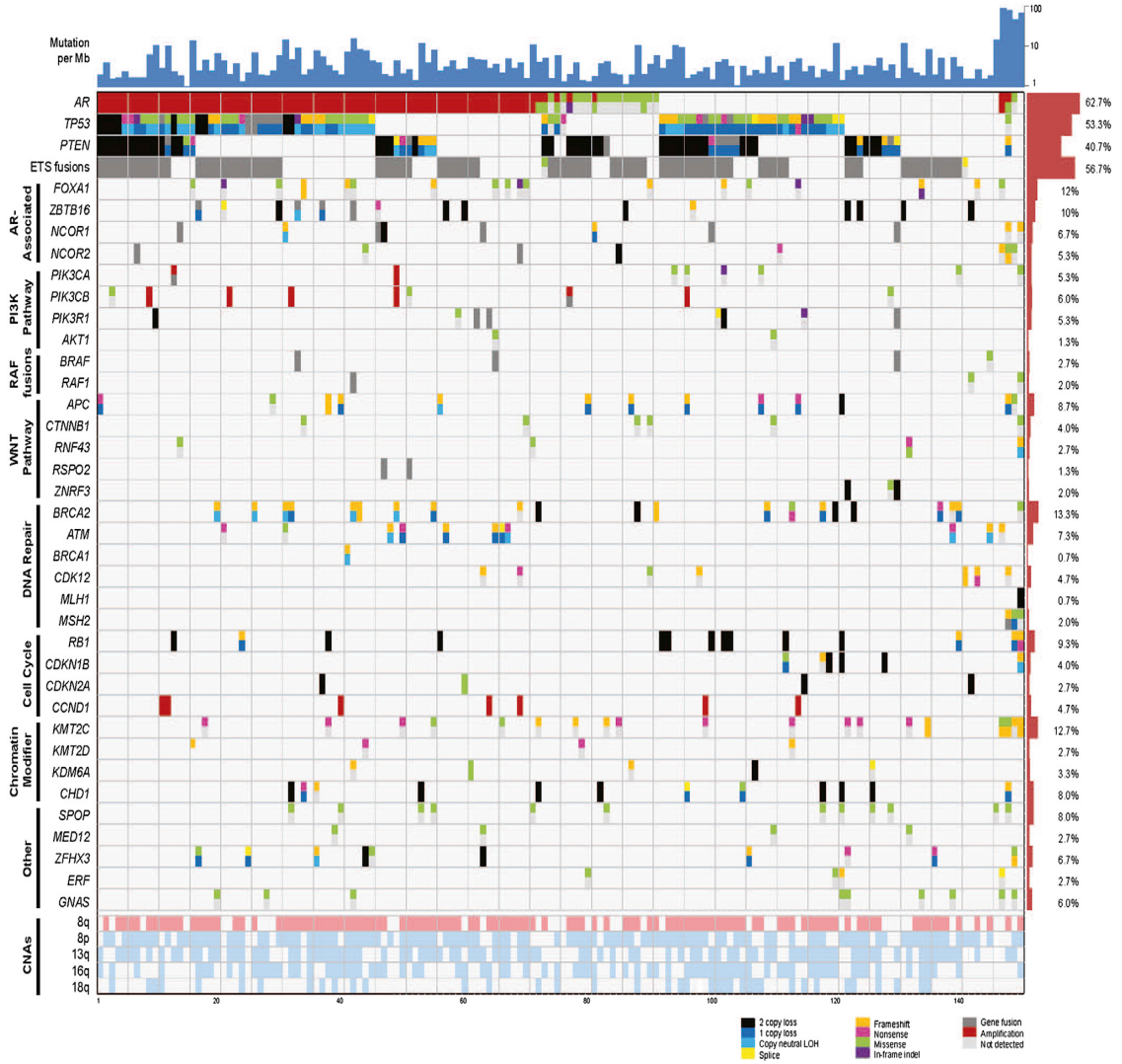


The Changing Landscape of Prostate Cancer in 2021



Integrative landscape analysis of somatic and germline aberrations in mCRPC

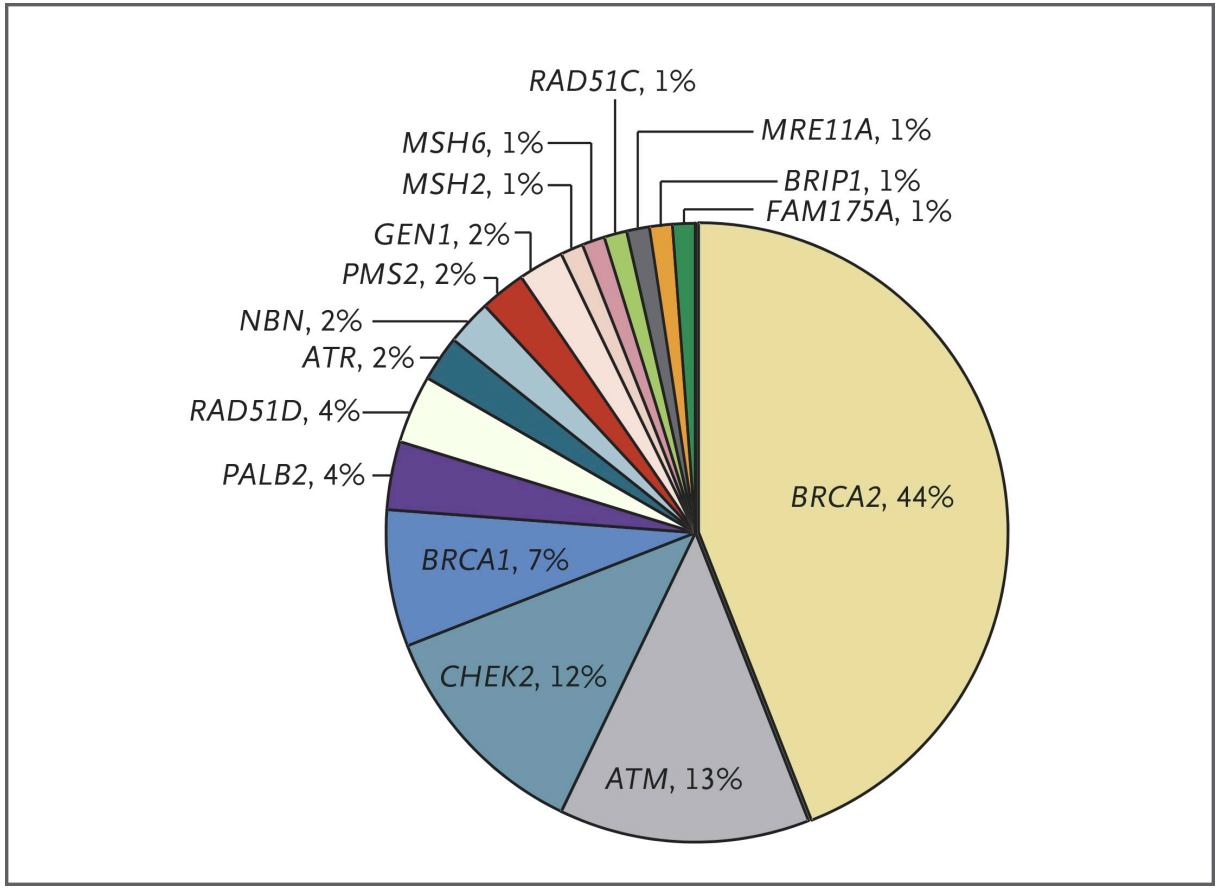
- Multi-institutional prospective biopsies
- 90% of mCRPC harbor clinically actionable molecular alterations
- 23% of mCRPC harbor DNA repair pathway aberrations
- 8% harbor germline mutations



Robinson D et al. *Cell*. 2015;161:1215-28

Distribution of presumed pathogenic germline mutations

Incidence of germline mutations in genes mediating DNA-repair: 11.8%

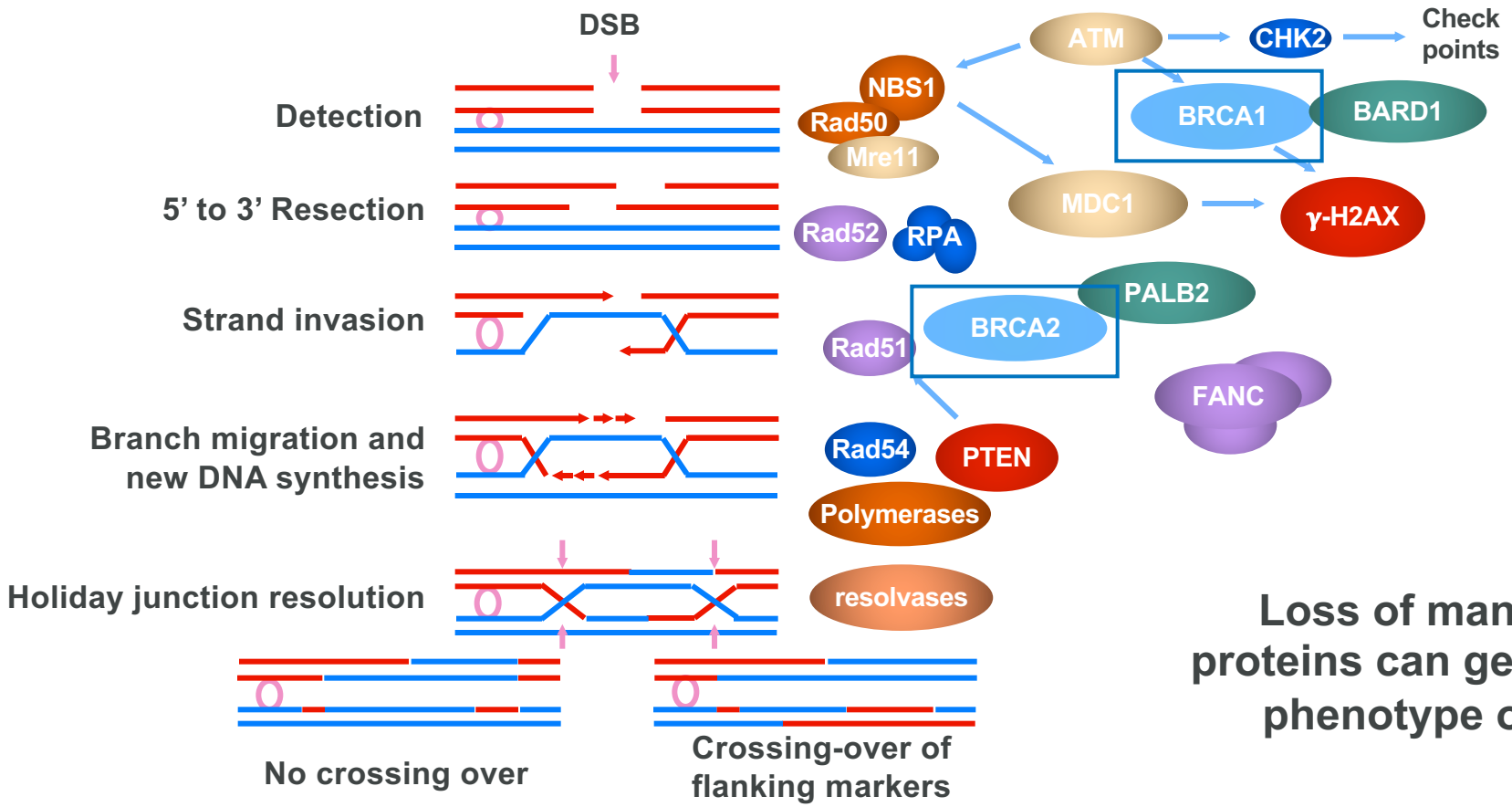


Distribution of 16 germline mutations

692 men with documented metastatic prostate cancer who were unselected for family history of cancer or age at diagnosis

Pritchard CC et al. N Engl J Med 2016;375:443-53

Homologous recombination DNA repair requires multiple proteins not just BRCA1/2



Loss of many DNA repair proteins can generate the same phenotype of BRCA*ness*

Presented By Peter Nelson at 2016 ASCO Annual Meeting; Pritchard CC et al. N Engl J Med 2016;375:443-53

- Germline and tumor NGS testing of DNA repair genes is increasingly recommended to guide advanced prostate cancer treatment

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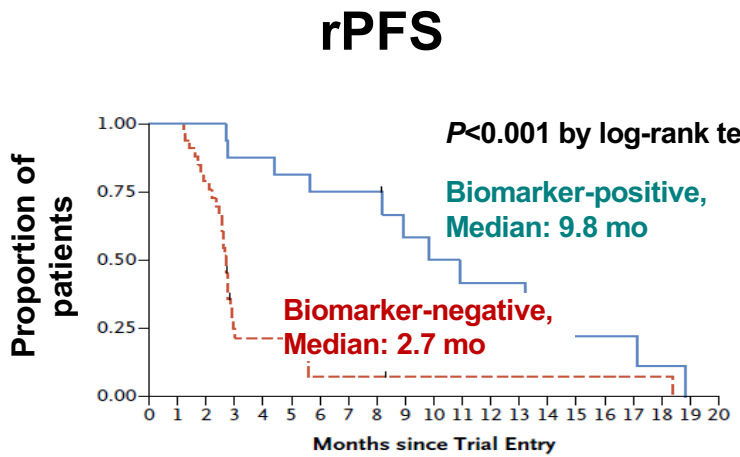
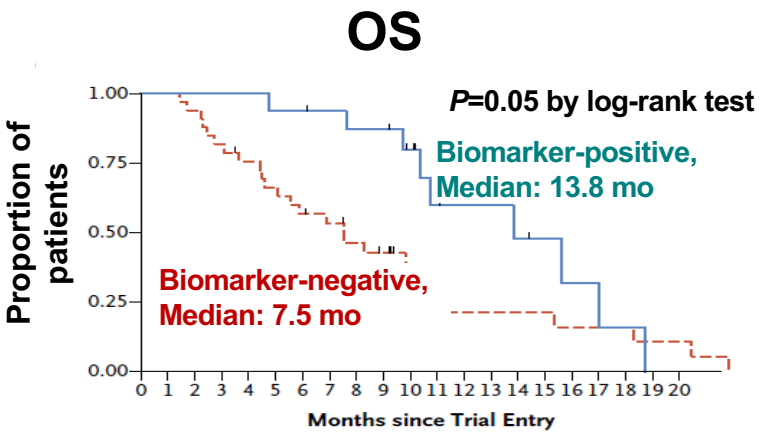
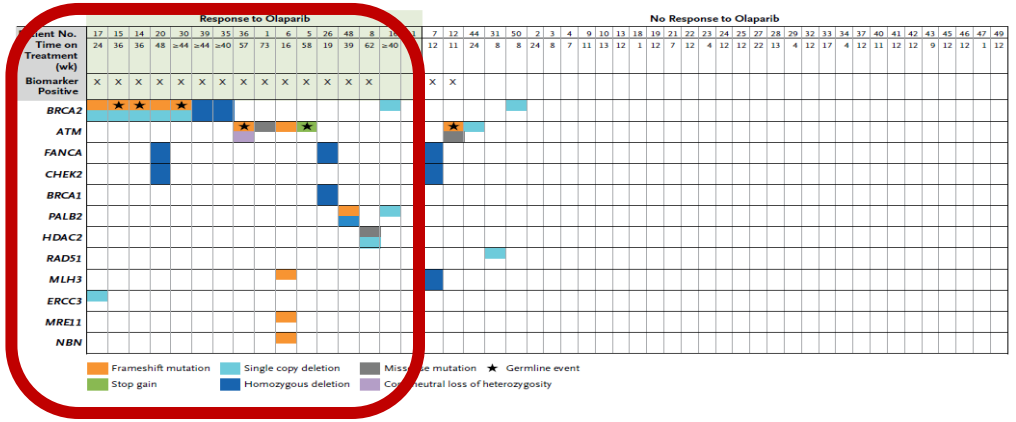
Defects in DNA repair genes (DRG) associated with PARP inhibitor sensitivity: Olaparib







- 49 heavily pretreated mCRPC men
- PARP inhibitor (olaparib 400 mg bid)
- **Genomic signature of PARP inhibitor sensitivity in 16/49 (33%)**
  - BRCA2, ATM, BRCA1, PALB2, CHEK2, FANCA, HDAC2
  - **Response to PARP in 14/16**

bid: twice daily; OS: overall survival; rPFS: radiographic progression-free survival

Mateo J et al. N Engl J Med 2015;373:1697-708

PROfound Phase III Trial design

Key eligibility criteria

- mCRPC with disease progression on prior NHA eg abiraterone or enzalutamide
- Alterations in ≥1 of any qualifying gene with a direct or indirect role in HRR

Cohort A
BRCA1, *BRCA2* or *ATM*
N=245

- Olaparib 300 mg bid n=162
- Control* n=83

Cohort B
Other alterations
N=142

- Olaparib 300 mg bid n=94
- Control* n=48

2:1 randomization
Open-label

Upon BICR progression, control patients were allowed to cross over to olaparib

Stratification factors
- Previous taxane
- Measurable disease

Statistical analysis plan

Primary endpoint
rPFS by BICR in Cohort A
(alpha=0.05)

Confirmed ORR by BICR in Cohort A
(alpha=0.05)

rPFS by BICR in Cohorts A+B
(alpha=0.05)

Time to pain progression in Cohort A
(alpha=0.05)

OS in Cohort A Interim
(alpha=0.01)

OS in Cohort A Final
(alpha=0.047)

Key secondary endpoints

Patients randomized between April 2017 and November 2018; DCO for final OS: 20 March 2020

*Control either enzalutamide (160 mg qd) or abiraterone (1000 mg qd + prednisone [5 mg bid]).
BICR, blinded independent central review; bid, twice daily; DCO, data cut-off; ORR, objective response rate; qd, once daily; RECIST, Response Evaluation Criteria In Solid Tumours.

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Background

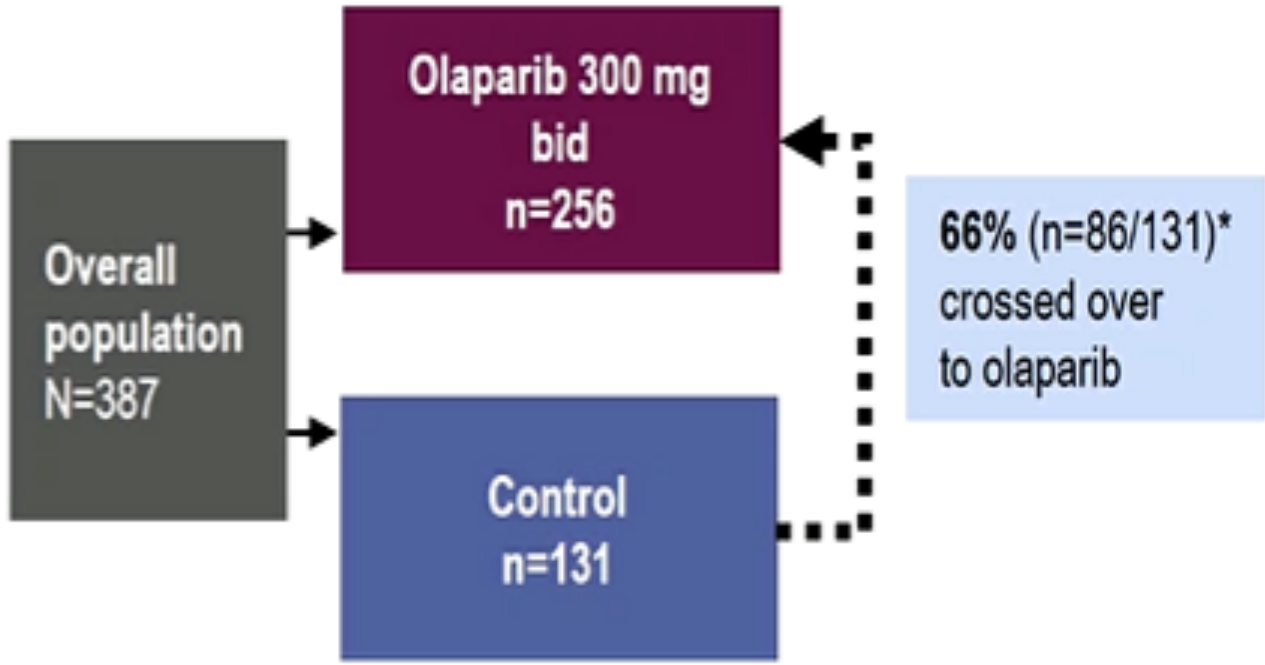
- 20–30% of mCRPCs harbour deleterious alterations in DNA damage repair genes with direct or indirect roles in HRR[1–7]
- PROfound used a clinical trial assay (based on FoundationOne® CDx) to prospectively select patients harbouring alterations in *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/or *RAD54L* in tumour biopsies
- PROfound is **the first positive Phase III PARPi trial in mCRPC**, meeting its primary endpoint of prolonged rPFS for mCRPC with alterations in *BRCA1*, *BRCA2* or *ATM* progressing on prior NHA and treated with olaparib vs enzalutamide or abiraterone (control; HR 0.34)
  - Improved rPFS was also observed in the overall population (HR 0.49)[8]
- **Olaparib improved multiple clinical/patient-reported endpoints** and is FDA approved for mCRPC with alterations in multiple DNA repair genes post-enzalutamide/abiraterone*
- Despite crossover, olaparib had a favourable trend for OS at interim analysis; **we now present final OS**

**PPP2R2A* is excluded from the FDA label. The role of *PPP2R2A* as an HRR gene could not be validated preclinically.
FDA, US Food and Drug Administration; HR, hazard ratio; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, next-generation hormonal agent; OS, overall survival; PARPi, inhibitor; poly(ADP-ribose) polymerase (PARP) inhibitor; rPFS, radiographic progression-free survival.

1. Robinson D *et al. Cell* 2015;161:1215–28; 2. Pritchard CC *et al. N Engl J Med* 2016;375:443–53; 3. Abida W *et al. JCO Precis Oncol* 2017; 4. Abida W *et al. Ann Onc* 2018;29:abstract 793PD; 5. Smith MR *et al. J Clin Oncol* 2019;37:abstract 202; 6. Mateo J *et al. N Engl J Med* 2015;373:1697–708; 7. Mateo J *et al. Lancet Oncol* 2020;21:162–74; 8. de Bono J *et al. N Engl J Med* 2020;382:2091–102.

Patients in the control arm had the option to cross over to olaparib if they met the following criteria:

- Radiographic disease progression
- No other subsequent anticancer therapy
- Any toxicities from prior therapy grade ≤1
- Agreement to continue with study visit schedule



Prespecified sensitivity analysis of OS adjusting for the impact of patients in the control arm receiving subsequent olaparib treatment was conducted using RPSFTM

*83 patients with disease progression crossed over per-protocol, and three additional patients received olaparib outside of the study.
RPSFTM is a statistical method that can be used to adjust for the impact of patient crossover on long-term outcomes in randomized controlled trials.[1]
More information on the selection of RPSFTM based on an interim analysis of OS can be found in the Agarwal *et al.* poster 622P presented at this meeting.
NICE, National Institute for Health Care Excellence; RPSFTM, rank-preserving structural failure time models.
1. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching 2014.

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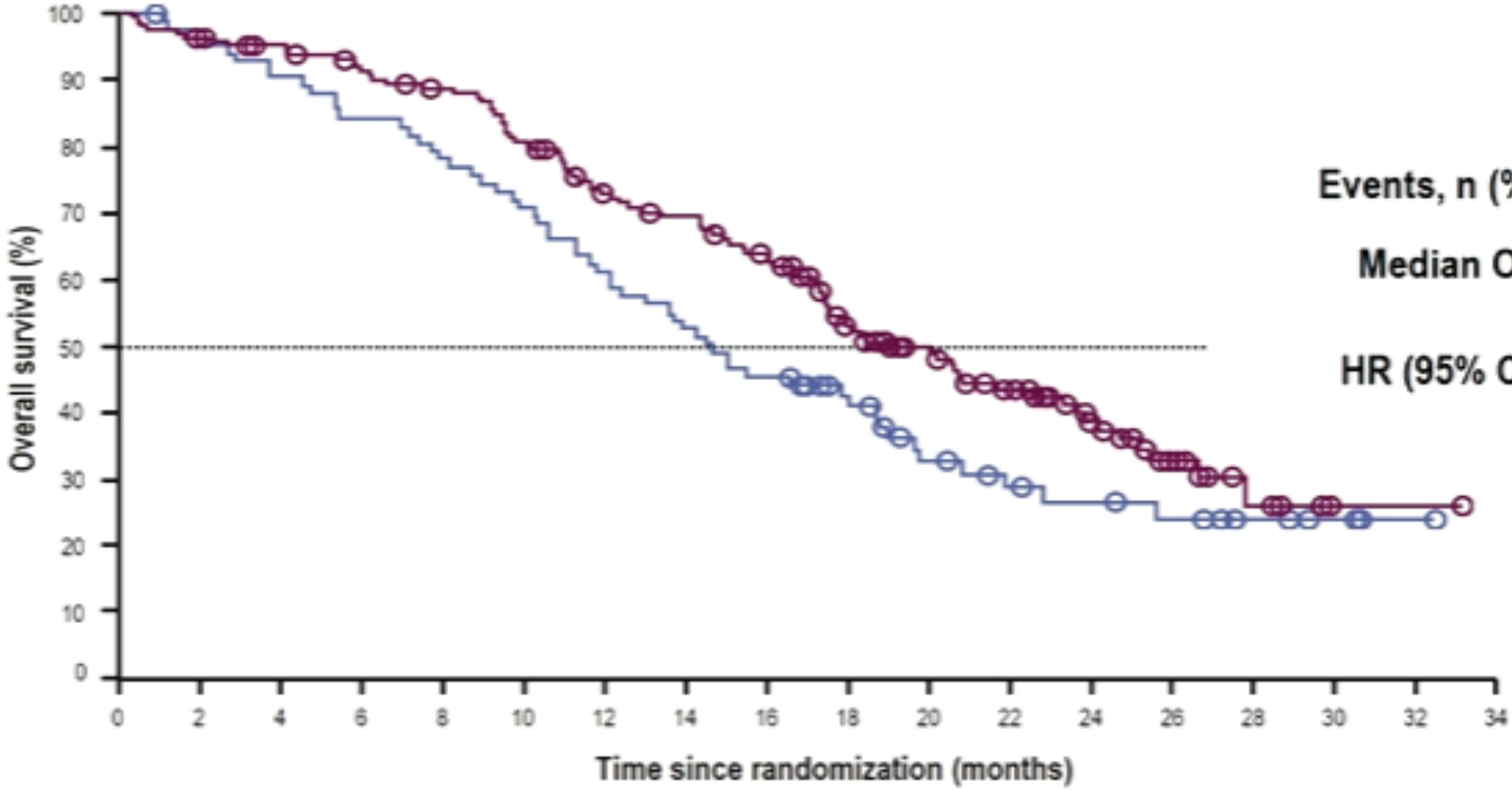
Olaparib improved OS in Cohort A

BRCA1, *BRCA2* or *ATM* mCRPC (final prespecified analysis)



No. at risk

Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	74	69	64	58	50	43	37	27	18	15	11	9	6	3	1	0

	Olaparib (N=162)	Control (N=83)
Events, n (%)	91 (56)	57 (69)
Median OS	19.1 months	14.7 months
HR (95% CI)	0.69 (0.50–0.97); *P*=0.0175*	

*0.047 alpha spent at the final OS analysis. Median follow-up duration for censored patients was 21.9 months in the olaparib arm and 21.0 in the control arm.
CI, confidence interval.

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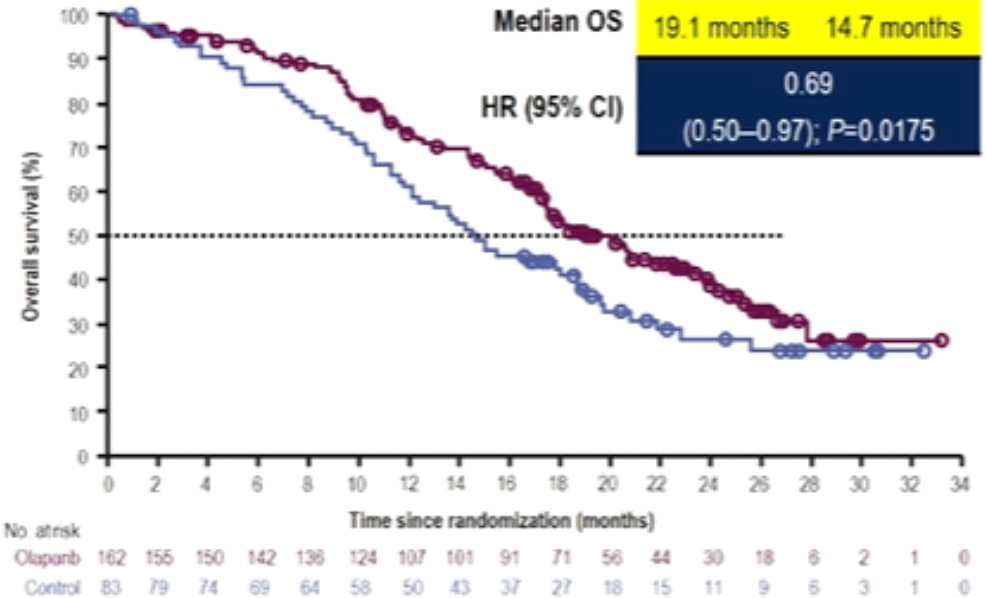
Olaparib improved OS in Cohort A (*BRCA1*, *BRCA2* or *ATM*)

Prespecified adjustment for crossover (final prespecified analysis)

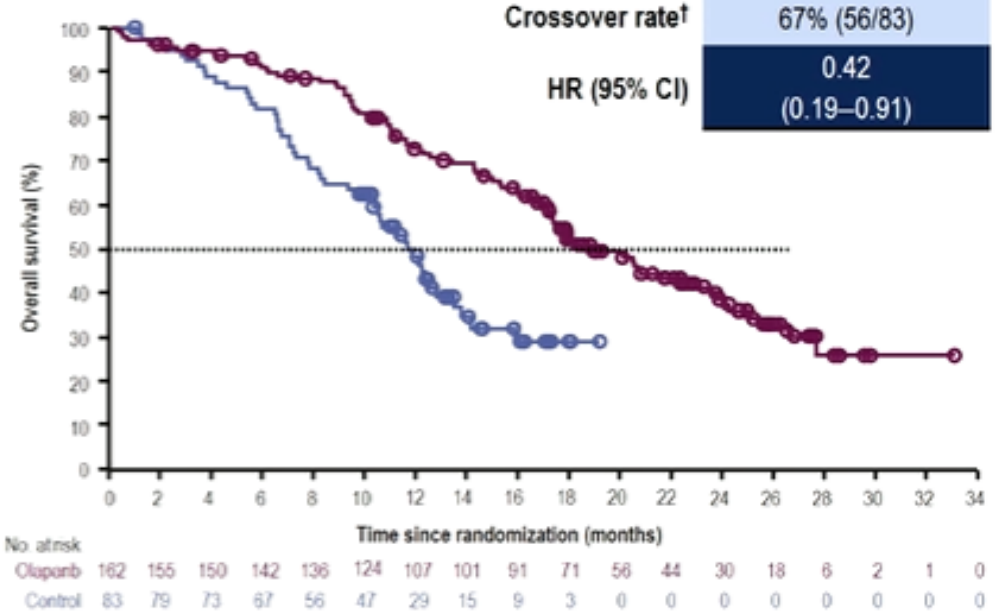
Cohort A

	Olaparib (N=162)	Control (N=83)
Events, n (%)	91 (56)	57 (69)
Median OS	19.1 months	14.7 months
HR (95% CI)	0.69 (0.50–0.97); *P*=0.0175	



Cohort A with adjustment for crossover*

Crossover rate†	67% (56/83)
HR (95% CI)	0.42 (0.19–0.91)



Median follow-up duration for censored patients was 21.9 months for the olaparib arm and 21.0 months for the control arm.
*Re-censored; conducted using RPSFTM to demonstrate the impact on OS of crossover of patients from the control arm to receive olaparib as a first subsequent anticancer therapy. †Patients receiving olaparib at any time.

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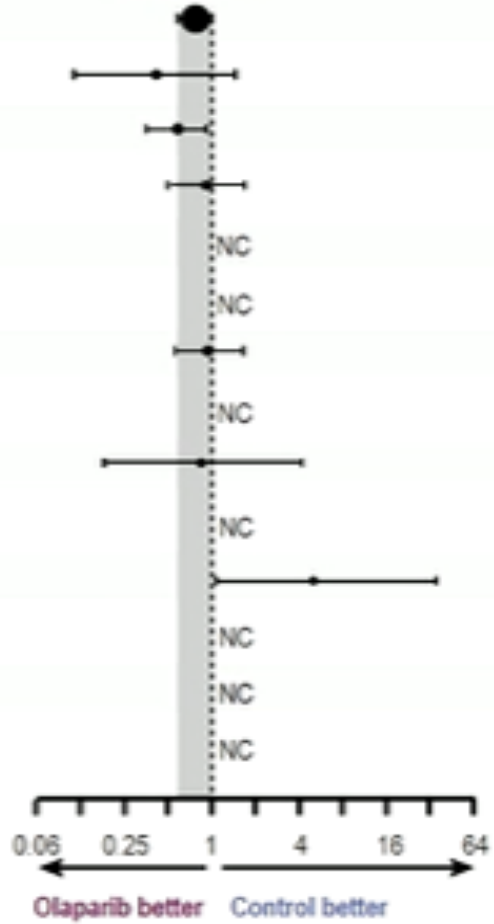
Exploratory gene-level analyses of final OS

	Subgroup	Olaparib n/N	Control n/N	HR (95% CI)
	Alteration in any single HRR gene	148/239	81/120	0.79 (0.60–1.04)
Cohort A	*BRCA1* (n=13)	5/8	5/5	0.42 (0.12–1.53)
Cohort A	*BRCA2* (n=128)	39/81	32/47	0.59 (0.37–0.95)
Cohort A	*ATM* (n=86)	39/62	15/24	0.93 (0.53–1.75)
Cohort B	*BARD1* (n=1)	0/0	1/1	NC
Cohort B	*BRIP1* (n=3)	1/2	1/1	NC
Cohort B	*CDK12* (n=89)	47/61	18/28	0.97 (0.57–1.71)
Cohort B	*CHEK1* (n=2)	1/1	0/1	NC
Cohort B	*CHEK2* (n=12)	4/7	3/5	0.87 (0.19–4.44)
Cohort B	*PALB2* (n=4)	2/3	1/1	NC
Cohort B	*PPP2R2A* (n=10)	5/6	2/4	5.11 (1.10–35.73)
Cohort B	*RAD51B* (n=5)	2/4	1/1	NC
Cohort B	*RAD51D* (n=1)	1/1	0/0	NC
Cohort B	*RAD54L* (n=5)	2/3	2/2	NC



Patients with tumours harbouring a *BRCA1* or *BRCA2* alteration appeared to derive the greatest OS benefit from olaparib

Data are reported only for patients with an alteration in a single gene. HR and CI values were not calculated for subgroups in which fewer than five survival events occurred; none of the enrolled patients harboured alterations in *FANCL* or *RAD51C*. The sizes of the circles are proportional to the number of events.

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Conclusions

- In men with mCRPC pretreated with a prior NHA, there was **significantly improved OS with olaparib** vs enzalutamide/abiraterone in Cohort A **(*BRCA1*, *BRCA2*, and/or *ATM* altered mCRPC; 19.1 months vs 14.7 months; HR 0.69; *P*=0.0175)** despite crossover (n=56, 67%) from the control arm to olaparib
- Prespecified sensitivity analyses, adjusting for the impact of crossover, suggest that the treatment effect of olaparib is likely to be greater than what has been observed in PROfound
- In the overall population (alterations in any of the 15 prespecified DDR genes), olaparib treatment is associated with a non-statistically significant improvement in OS
- Additional studies are required to further delineate genomic indicators of response to PARP inhibition
- The safety profile of olaparib was consistent with the primary analysis[1]
- **PROfound is the first randomized trial to prospectively demonstrate OS improvement in a molecularly-defined subset of prostate cancer, supporting the implementation of genomic testing in clinical practice**

DDR, DNA damage repair

1. de Bono J *et al. N Engl J Med* 2020;382:2091–102.

Phase II Trial of Rucaparib in Patients with Metastatic Hormone Sensitive Prostate Cancer Harboring Germline DNA Repair Gene Mutations (TRIUMPH)

Rucaparib in mHSPC: Inclusion / Exclusion Criteria

- ***Germline*** mutation in one or more homologous recombination DNA-repair genes (BRCA1, BRCA2, ATM, CHEK2, NBN, RAD50, RAD51C, RAD51D, PALB2, MRE11, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM) as documented by a clinical CLIA-grade, saliva or blood-based (i.e leukocyte DNA) genetic test (including but not limited to Invitae, Color Genomics, etc).
- All patients must be ineligible for or have declined ADT-based systemic treatment
- Absolute PSA ≥2.0 ng/ml at screening.
- Radiographic evidence of metastatic disease by CT scan and bone scan
- Serum testosterone ≥ 100 ng/dl

Objectives

- Primary objective:
  - PSA response rate to rucaparib (*confirmed PSA_{50} response*)

- Secondary objectives:
  - To estimate the median PSA progression-free survival (PCWG3).
  - To estimate the median progression-free survival (PCWG3).
  - To estimate the objective response rate (ORR).
  - To determine the safety/tolerability of rucaparib in the mHSPC population.

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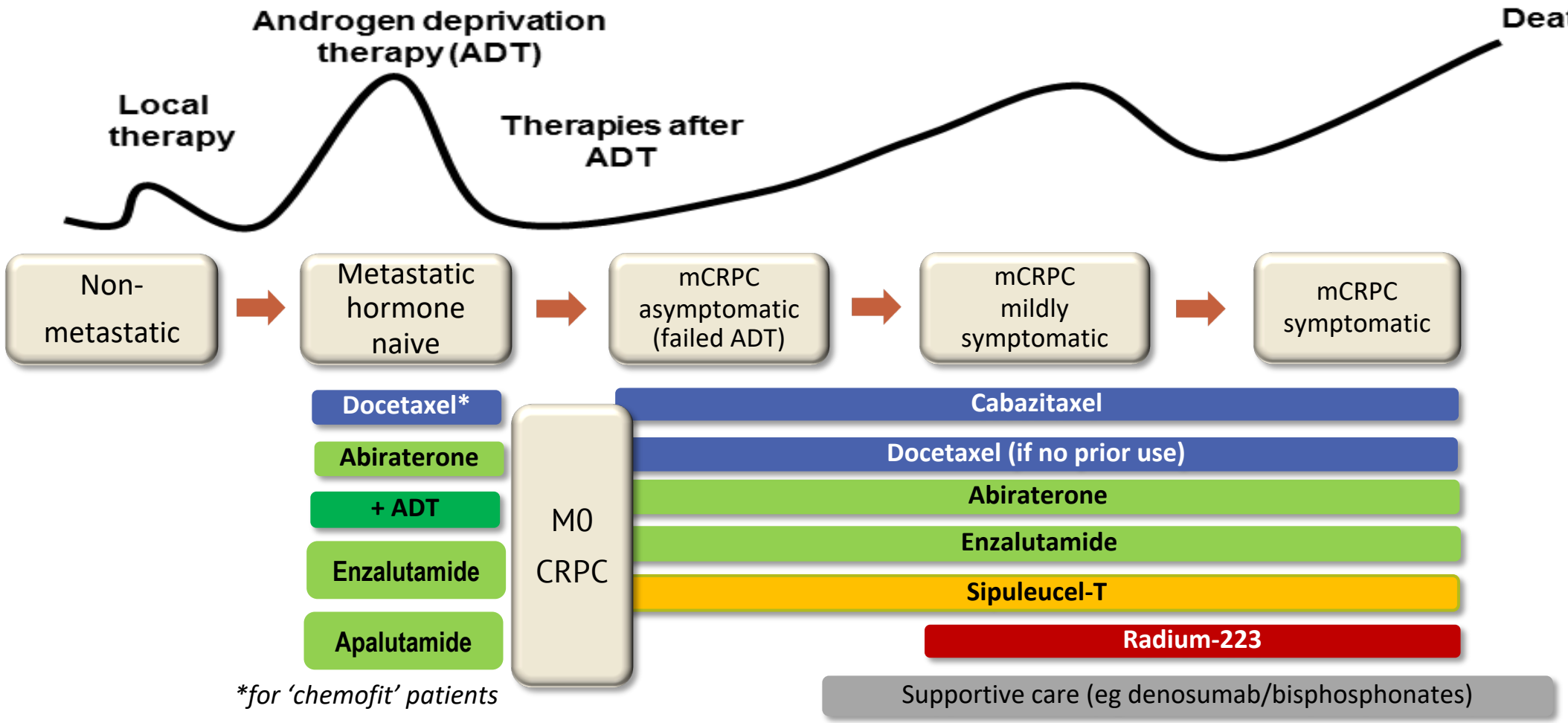
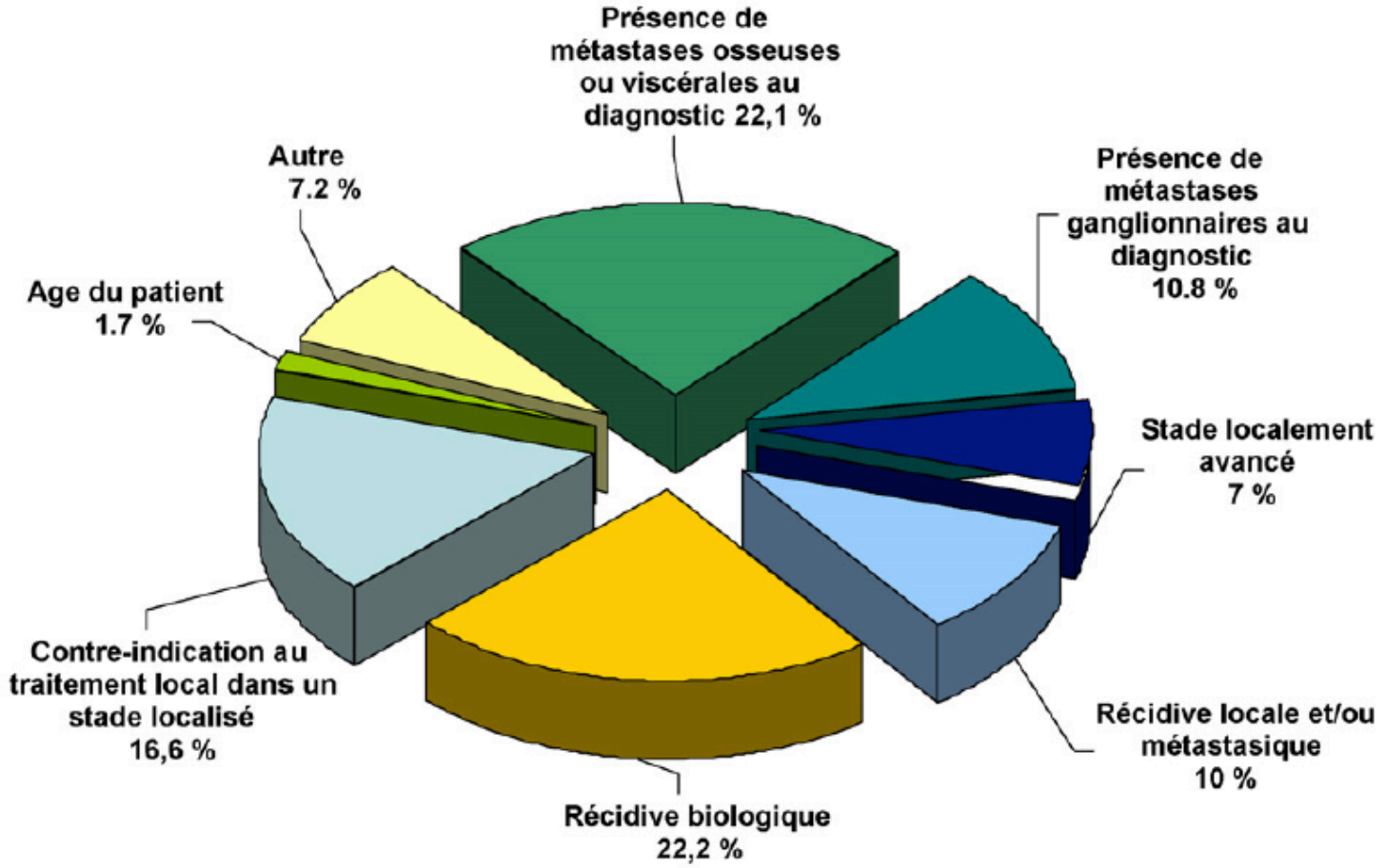


Androgen Deprivation Therapy Prescribed to a Heterogeneous Population



A. de la Taille, Progrès en urologie (2009) 19, 313-320

PROSPER Study Design

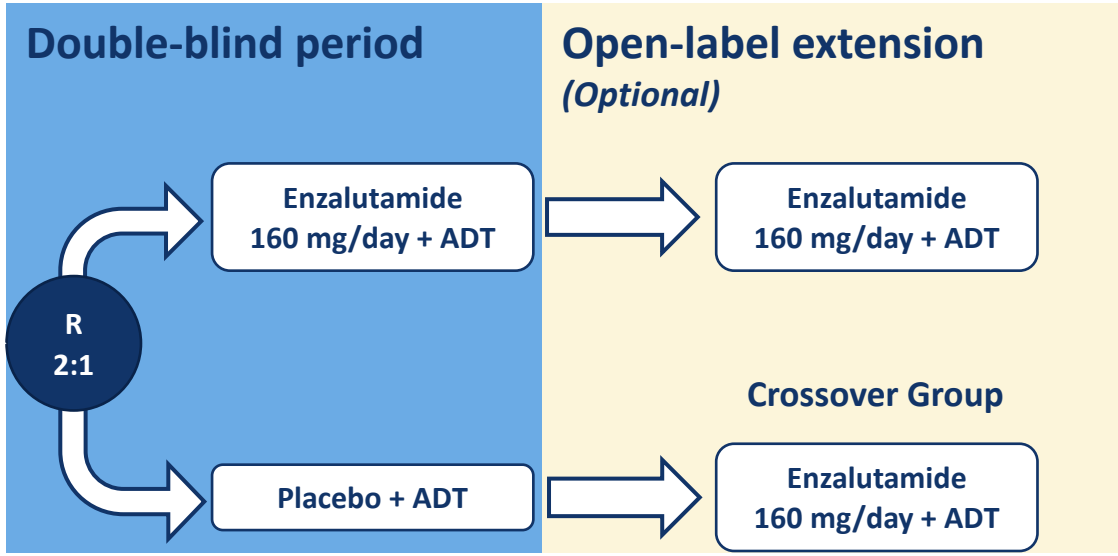
Key Eligibility Criteria

- nmCRPC (central review)
- Rising PSA despite castrate testosterone level (≤ 50 ng/dL)
- Baseline PSA ≥ 2 ng/mL
- PSA doubling time ≤ 10 months

Stratification

- PSA doubling time (< 6 mo vs 6-10 mo)
- Baseline use of bone-targeting agent (Y/N)

N = 1401



Primary endpoint

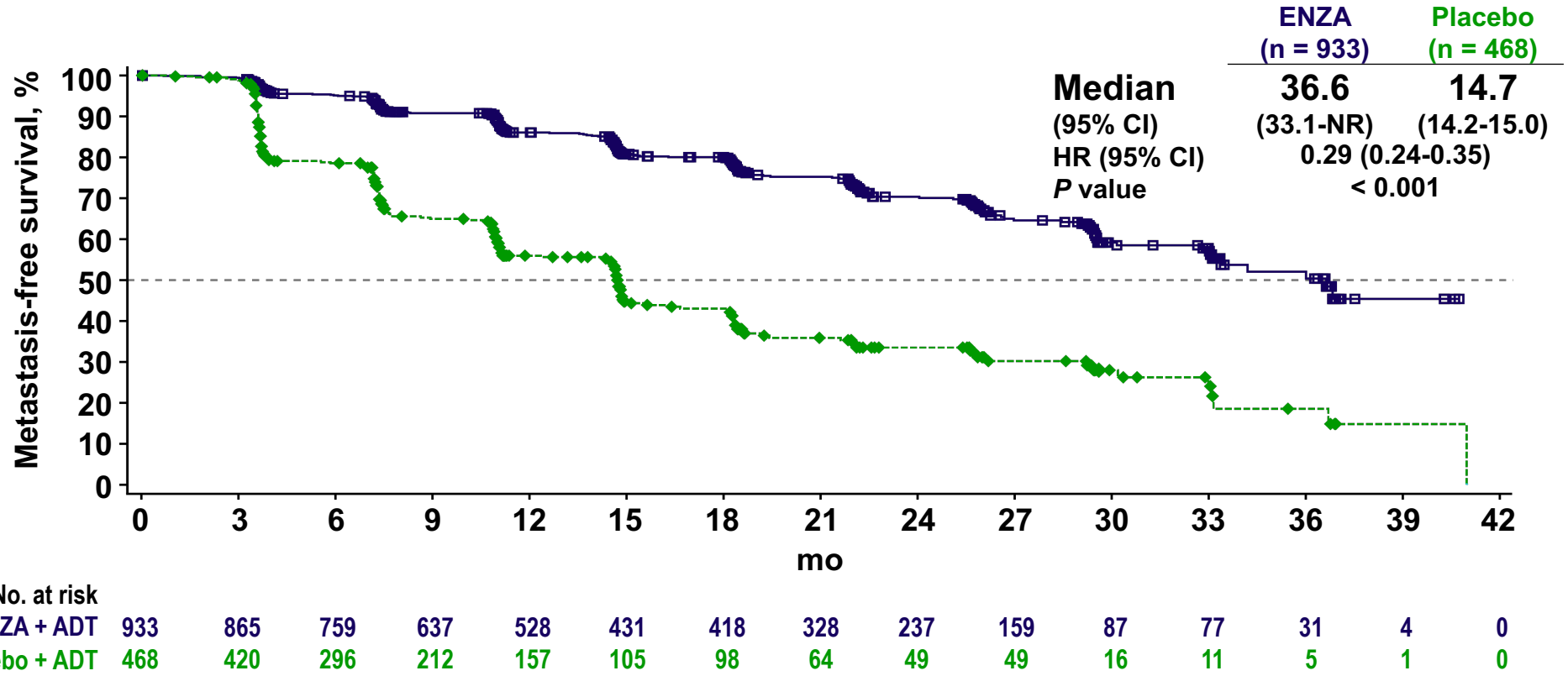
- MFS (defined as time from randomization to radiographic progression or death within 112 days of treatment discontinuation without evidence of radiographic progression)

Secondary endpoints

- OS
- Time to PSA progression
- Safety
- PSA response
- Quality of life

ADT, androgen deprivation therapy; MFS, metastasis-free survival; nmCRPC, nonmetastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; R, randomization.

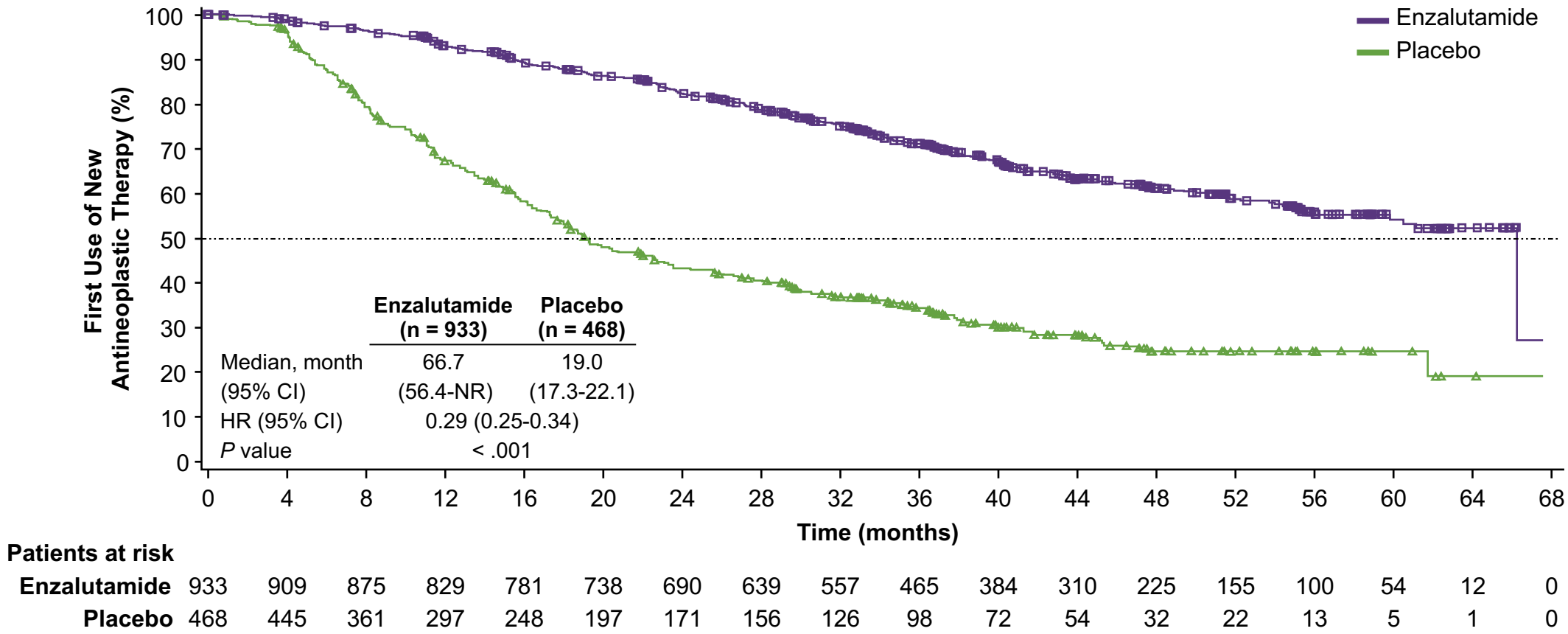
Primary Endpoint: MFS



- The median follow-up was 18.5 mo for the enzalutamide group and 15.1 mo for the placebo group
- Enzalutamide treatment resulted in a 71% lower risk of radiographic progression or death than did placebo

CI, confidence interval; ENZA, enzalutamide; NR, not reached.
Adapted from Hussain M, et al. *N Engl J Med*. 2018;378:2465-2474.

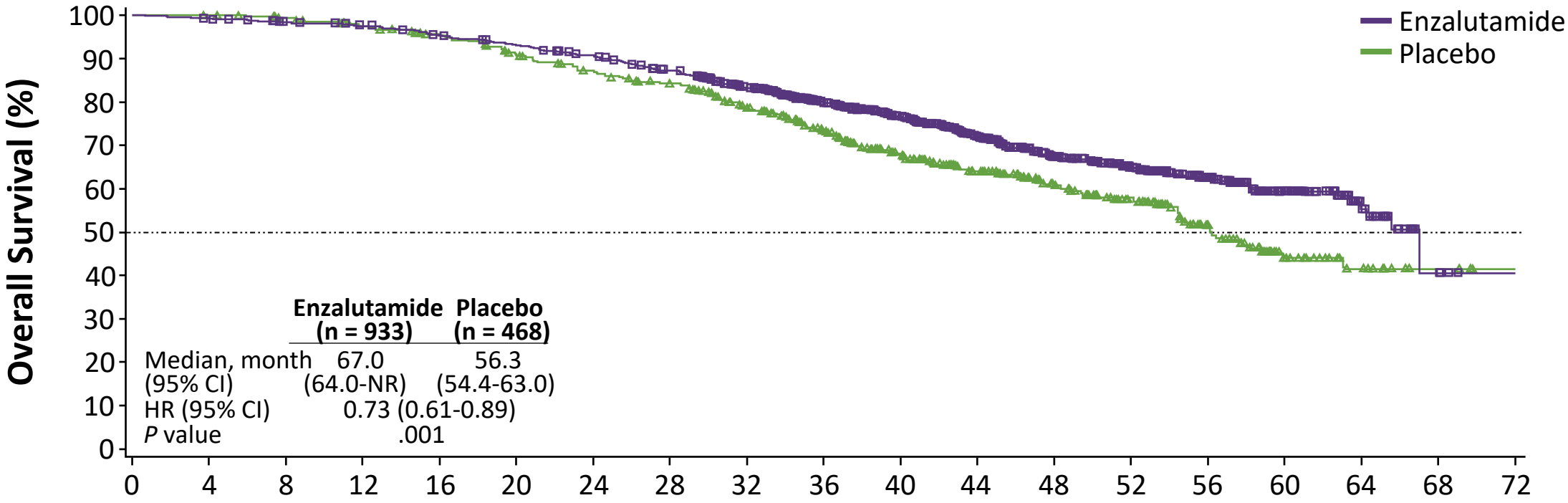
PROSPER Time to First Use of Subsequent Antineoplastic Therapy



CI, confidence interval; HR, hazard ratio; NR, not reached.

PROSPER Final Overall Survival Analysis

Enzalutamide was associated with a statistically significant 27% reduction in the risk of death



	Enzalutamide (n = 933)	Placebo (n = 468)
Median, month (95% CI)	67.0 (64.0-NR)	56.3 (54.4-63.0)
HR (95% CI)	0.73 (0.61-0.89)	
P value	.001	

Patients at risk

Enzalutamide	933	926	910	897	874	850	822	782	700	608	517	424	327	244	169	89	33	4	0
Placebo	468	467	459	444	428	404	381	363	321	274	219	177	140	106	64	30	16	3	0

CI, confidence interval; HR, hazard ratio; NR, not reached.

84% of Patients Assigned to Placebo Received at Least 1 Subsequent Antineoplastic Therapy

	Enzalutamide (n = 930)	Placebo (n = 465)
Patients taking ≥ 1 antineoplastic therapy after treatment discontinuation	**33%**	**65%**
Subsequent therapies used by ≥ 5% of patients in any treatment group*		
Abiraterone acetate	49%	59%
Docetaxel	60%	47%
Enzalutamide†	14%	**36%**
Cabazitaxel	15%	16%
Bicalutamide	9%	14%

*Percentages are based on the number of patients who received at least one antineoplastic agent after discontinuation of the trial regimen (310 in the enzalutamide group and 303 in the placebo group).
†A total of 87 patients who received enzalutamide in the crossover group after the trial was unblinded were not included in this analysis, since they received enzalutamide as open-label treatment. After inclusion of these 87 patients, the total number of patients randomly assigned to placebo who received at least one subsequent antineoplastic agent increased to 390 (84%), and the total number of patients who received subsequent treatment with enzalutamide was 196.

PROSPER Safety

		Enzalutamide + ADT (n = 930)		Placebo + ADT (n = 465)
Median duration of treatment, mo (range)		**33.9 (0.2-68.8)**		**14.2 (0.1-51.3)**
Any adverse event	94%	34 per 100 patient-years	82%	60 per 100 patient-years
Within the first 3 months	65%	—	52%	—
Within the first 6 months	76%	—	64%	—
Any grade ≥ 3 adverse event	48%	17 per 100 patient-years	27%	20 per 100 patient-years
Within the first 3 months	10%	—	5%	—
Within the first 6 months	15%	—	12%	—
Any serious adverse event	40%	14 per 100 patient-years	22%	16 per 100 patient-years
Any adverse event leading to discontinuation	17%	6 per 100 patient-years	9%	6 per 100 patient-years
Any adverse event leading to death	5%	2 per 100 patient-years	1%	< 1 per 100 patient-years

The NEW ENGLAND JOURNAL of MEDICINE

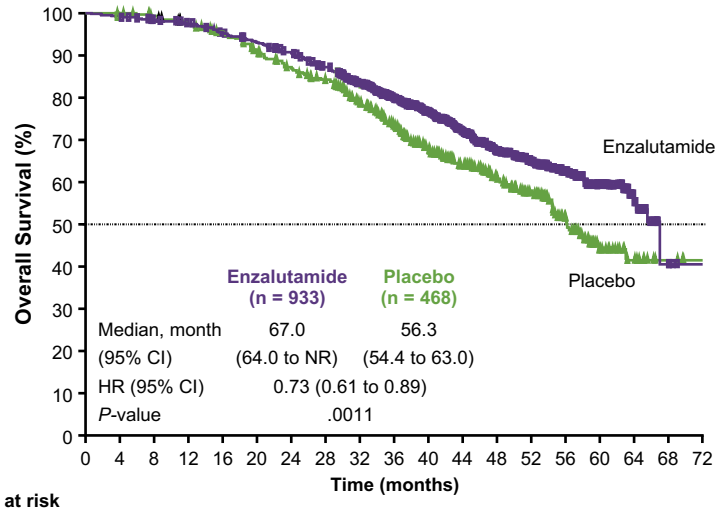
ORIGINAL ARTICLE

Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer

Cora N. Sternberg, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Neal D. Shore, M.D., Ugo De Giorgi, M.D., Ph.D., David F. Penson, M.D., M.P.H., Ubirajara Ferreira, M.D., Ph.D., Eleni Efstathiou, M.D., Ph.D., Katarzyna Madziarska, M.D., Ph.D., Michael P. Kolinsky, M.D., Daniel I. G. Cubero, M.D., Ph.D., Bettina Noerby, M.D., Fabian Zohren, M.D., Ph.D., Xun Lin, Ph.D., Katharina Modelska, M.D., Ph.D., Jennifer Sugg, M.S., Joyce Steinberg, M.D., and Maha Hussain, M.D., for the PROSPER Investigators*

Updated OS Data Available Across nmCRPC Trials

Enzalutamide – PROSPER[2]

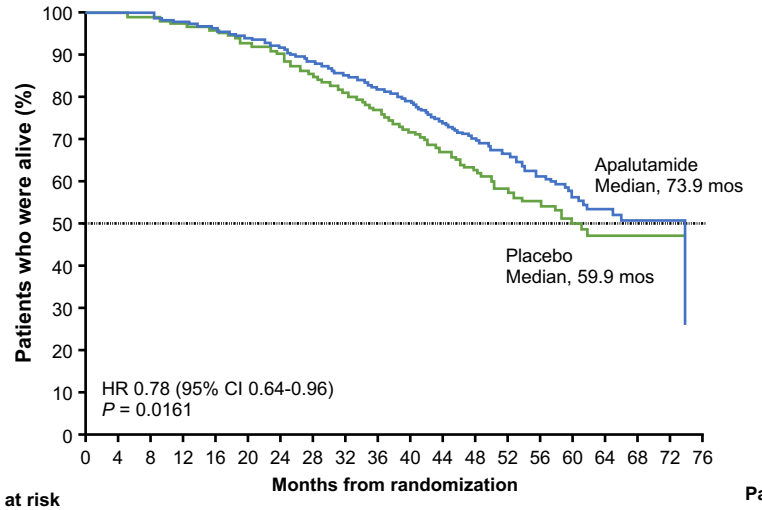


Patients at risk

Enzalutamide	933	926	910	897	874	850	822	782	700	608	517	424	327	244	169	89	33	4	0
Placebo	468	467	459	444	428	404	381	363	321	274	219	176	140	106	64	30	16	3	0

- **27%** reduction in risk of death
- **OS HR:** 0.73 (0.61-0.89)
- **Median OS:** 67.0 months ENZA vs. 56.3 months PBO
- **Median follow-up:** 48 mo

Apalutamide – SPARTAN[1]

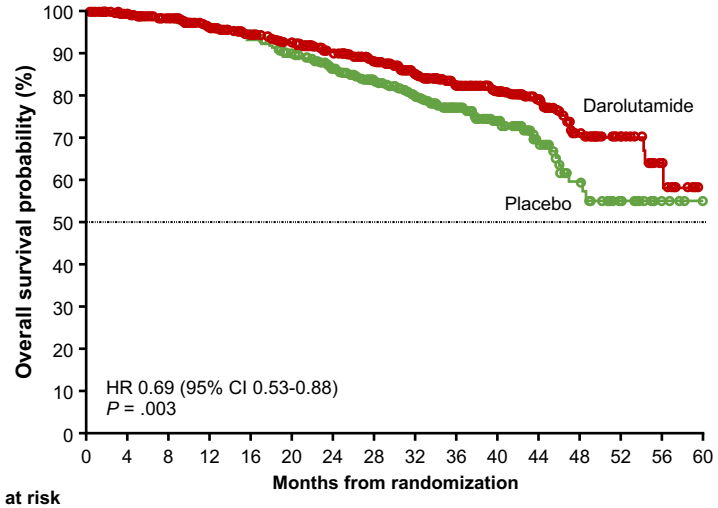


Patients at risk

Apalutamide	806	791	774	758	738	717	681	658	625	583	558	499	376	288	181	100	47	19	4	0
Placebo	401	392	386	373	358	339	328	306	286	263	245	204	156	114	82	38	21	6	2	0

- **22%** reduction in risk of death
- **OS HR:** 0.78 (0.64-0.96)
- **Median OS:** 73.9 months APA vs 59.9 months PBO
- **Median follow-up:** 52 mo

Darolutamide – ARAMIS[3]



Patients at risk

Darolutamide	955	932	908	863	816	771	680	549	425	293	214	129	69	37	12	0			
Placebo	554	530	497	460	432	394	333	261	182	130	93	54	28	16	4	0			

- **29%** reduction in risk of death
- **OS HR:** 0.71 (0.50-0.99)
- **Median OS:** Not reached
- **Median follow-up:** 29 mo

Enzalutamide, apalutamide, and darolutamide have not been studied in head-to-head trials.

1 Sternberg CN et al. *N Engl J Med*. 2020;382:2197-2206. 2. Smith MR et al, *Eur Urol.* 2020 Sep 6 [epub ahead of print]. 3. Fizazi K et al. *N Engl J Med* 2020;383:1040-1049.

Nonmetastatic CRPC: PROSPER Trial Updates

- In patients with nmCRPC, enzalutamide resulted in a clinically meaningful and statistically significant 27% lower risk of death than placebo
- Adverse events were consistent with the established safety profile of enzalutamide
- OS was similar across the 3 trials and MFS benefits were associated with improved OS
- **Results support that treating patients earlier is better!!**

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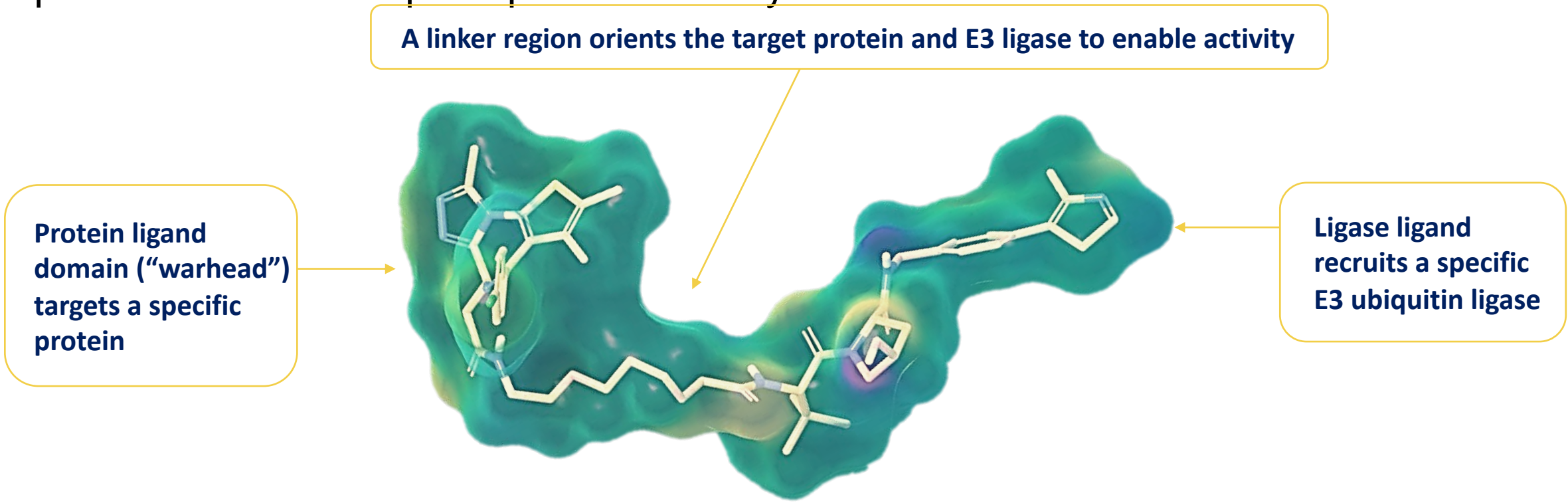
- Immunotherapy Trials: Merck and Magic 8
- NEPC
- Prostate Cancer Disparites: AA P-1000 and DoD

PROTAC® Protein Degraders

A proteolysis-targeting chimera (PROTAC®) degrader is a chimeric, modular small molecule engineered to induce the degradation of disease-causing proteins via the ubiquitin-proteasome system



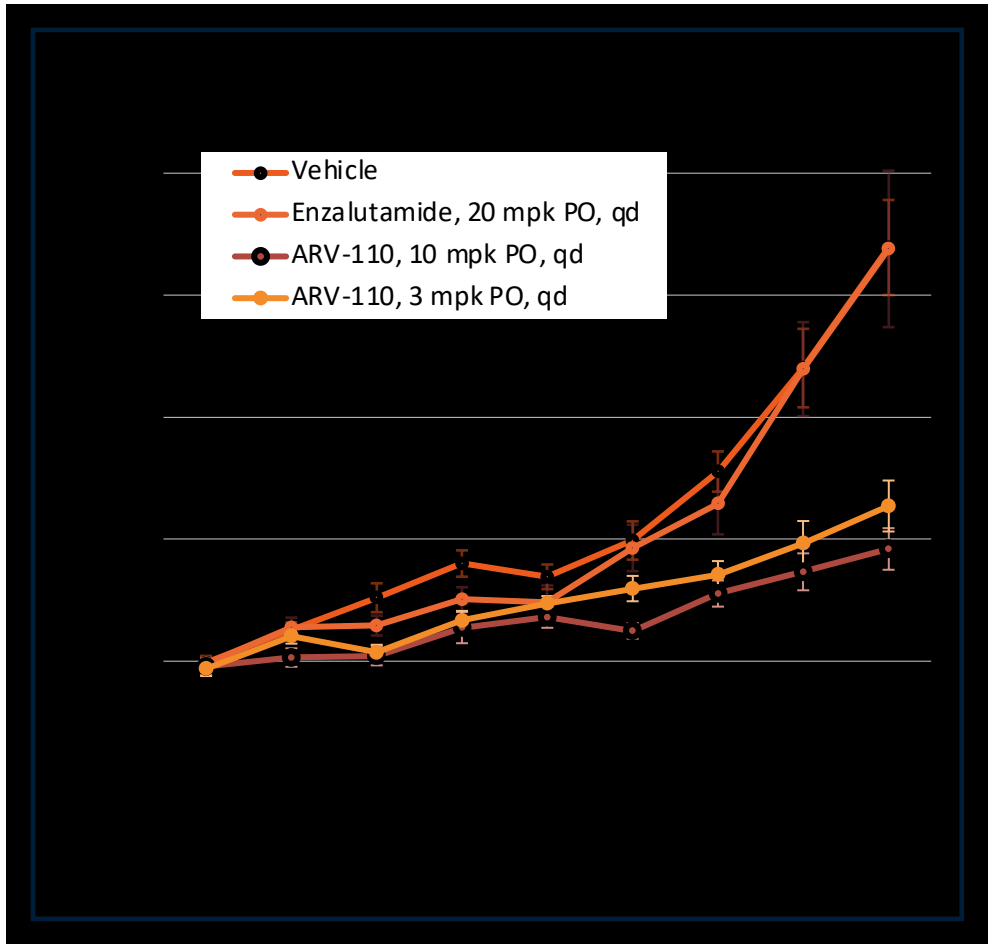
All three regions of the PROTAC® protein degrader play a role in the specificity and potency of target degradation

ARV 110: First-in-class AR PROTAC® Protein Degrader

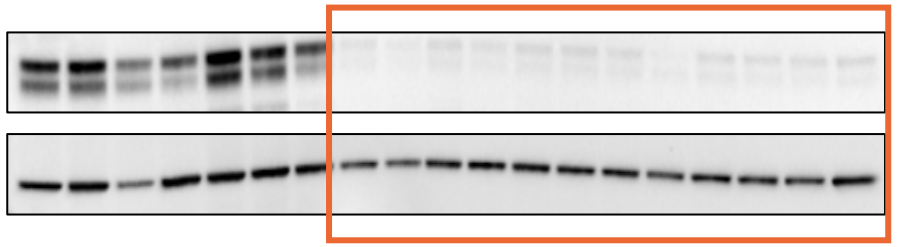
ARV-110 targets wildtype and altered AR protein

- *In vivo* activity in multiple xenograft models with:
  - AR gene amplification
  - AR mutation
  - Enzalutamide resistance (right) and insensitivity

- Degrades T878A, H875Y, F877L, and M895V point mutations but not L702H and AR-V7 in preclinical studies



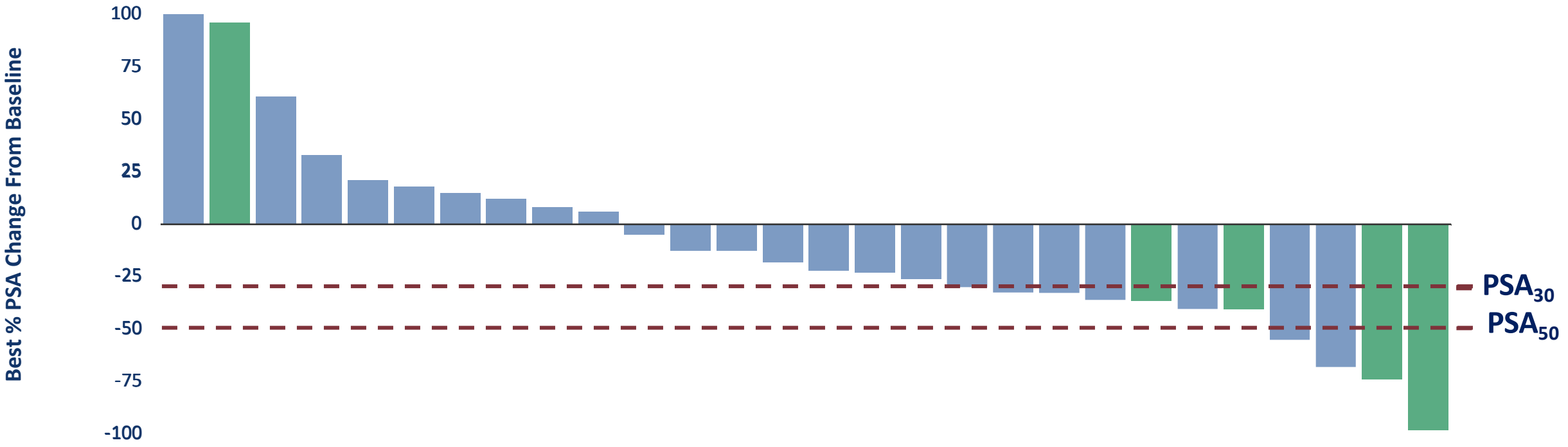
ARV-110 degrades ≥ 90% AR protein *in vivo*



MitoC: Western blot loading

In late stage, genetically heterogeneous population, have identified potential molecularly defined subgroups of patients sensitive to ARV-110

Best PSA Change In All Patients Above Minimum Exposure Threshold (N= 28) †††



AR Status	Amp	T878A, H875Y, L702H	Amp	WT	WT	Amp	Amp	WT	Amp	W742C	L702H	WT	WT	WT	WT	WT	WT	WT	Amp	WT	WT	T878A, T878S, L702H	WT	T878A, F877L, V716M, L702H	WT	WT	T878A, H875Y	T878A, H875Y
AR-V7††			+	+	+										+				+		+	+						
Other Genes Altered (n)	1	2	1	2	2	0	2†	1	2	4	3†	0	2	0	1	1†	0	2	1†	1	3	5†	0	6†	2	0	3	1

20/28 (71%) of patients have either T878/H875 or wild-type AR

Each column represents one patient. † Includes genes with multiple alterations, †† Epic Sciences, Genetic profiling: FoundationOne®Liquid (70-gene panel), ††† Data as of 30-Nov-2020.

ARDENT will evaluate efficacy in both late-line, molecularly defined patients, and in a broader, early-line mCRPC population

Features of the ARDENT Phase 2 Design **Total N = ~100**

- Enriches T878/H875 for exploration as a potential population for accelerated approval, and retains optionality for others
- Enrolls earlier, more AR-dependent populations
- Provides a subgroup for all screened patients

Patient Subgroup†	Tumor Characteristics
T878/H875	T878 and/or H875 AR mutated
Less-pretreated patients	Chemo-naïve, and progressed on abiraterone OR enzalutamide (*not both*)
Other AR degradable by ARV-110	AR wild type, amplified, and resistance-driving point mutations
AR not degradable by ARV-110	Tumors with L702H and AR-V7

† Tumors are heterogeneous, so patients may fall into multiple subgroups for post-hoc analysis.

Potential registrational paths

1. **Late-line (3L), molecularly defined mCRPC**

Potential for accelerated approval

2. **Earlier-line (1L/2L) mCRPC**

Via confirmatory study

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- **Immunotherapy Trials: Merck and Magic 8**
- NEPC
- Prostate Cancer Disparities: AA P-1000 and DoD

Immunotherapy with CPI and vaccines to date have offered limited efficacy in mCRPC

- Sipuleucel-T*
- Targeting CTLA-4: Ipilimumab: Final OS positive**
- G-VAX
- Prostvac
- Pembrolizumab after enzalutamide
- CDK12
- BiTEs , T cell engagers, CAR-T cells, ADCs

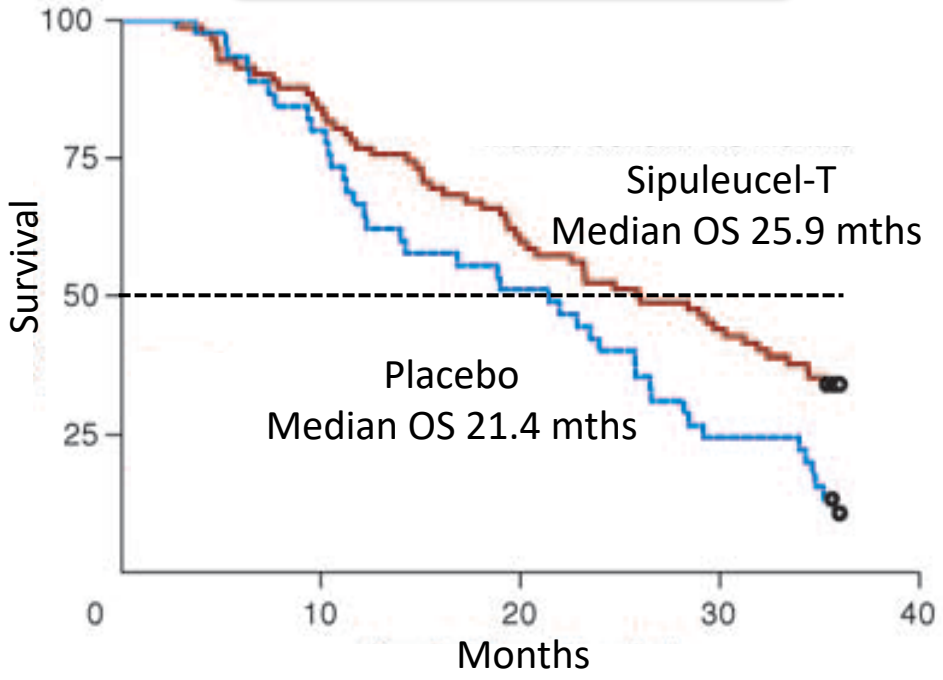
CPI: checkpoint inhibitors, mCRPC = metastatic castration-resistant prostate cancer; PSMA = prostate-specific membrane antigen

* Small EJ, J Clin Oncol 2009; 24: 3089-94,* Kantoff PW, NEJM 2010, 363: 411-22, **Fizazi K et al, Eur Urol Aug 20, 2020 (in press)

Sipuleucel-T improves overall survival in mCRPC

Phase III trial

HR (95% CI): 1.71 (1.13-2.58)
P= 0.010

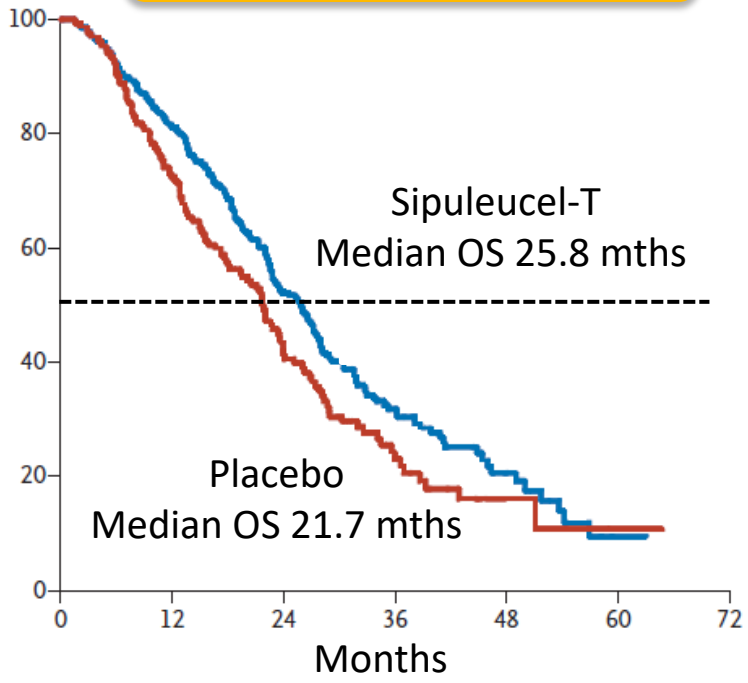


Sipuleucel-T (n = 82) vs Placebo (n=45)

Small EJ, J Clin Oncol 2009; 24: 3089-94

IMPACT phase III trial

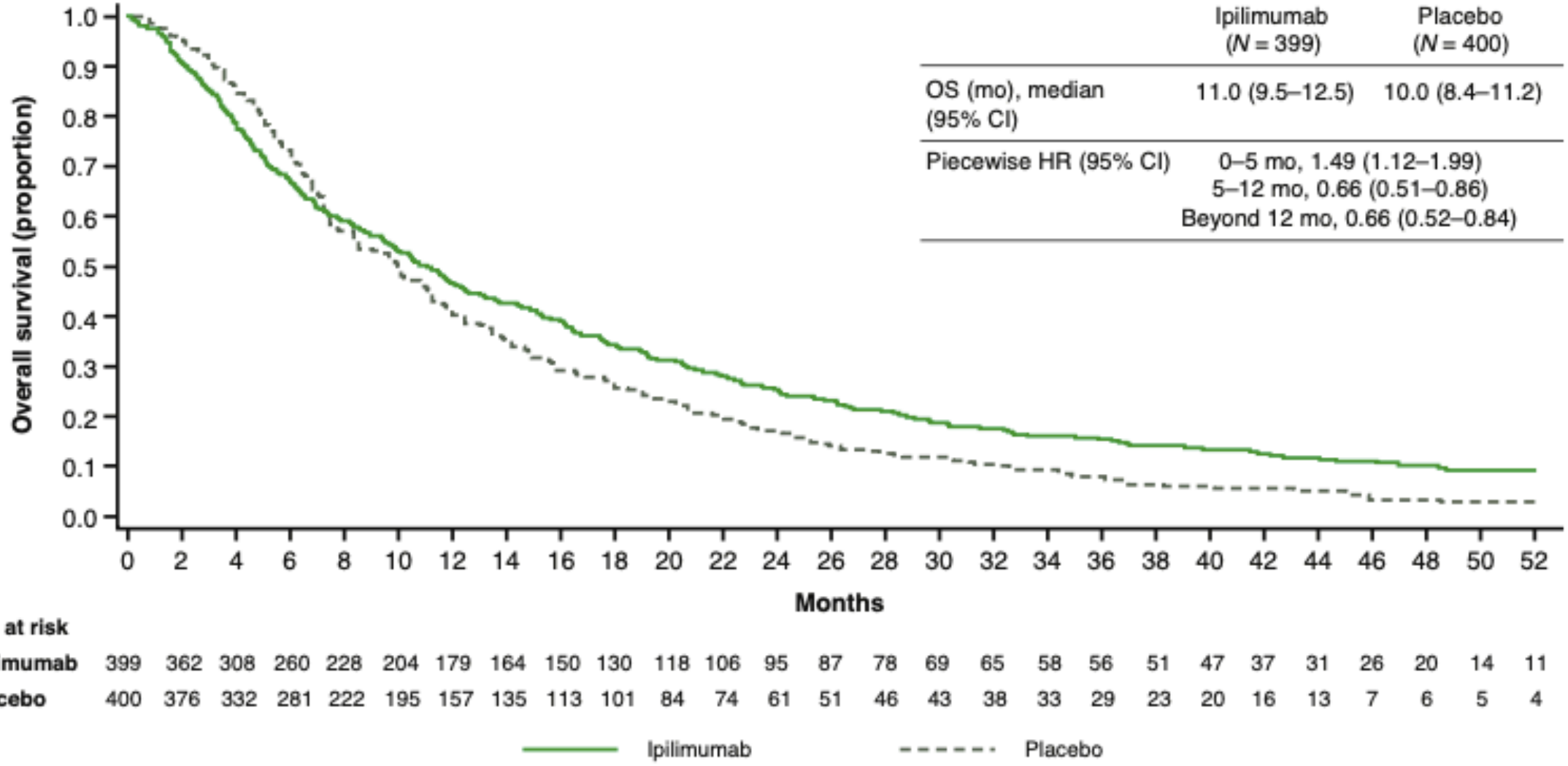
HR (95% CI): 0.78 (0.61-0.98)
P =0.032



Sipuleucel-T (n = 341) vs Placebo (n=171)

Kantoff PW, NEJM 2010, 363: 411-22

Final Analysis of the Ipilimumab vs Placebo Following Radiotherapy Phase III Trial in Post docetaxel mCRPC Identifies an Excess of Long-term Survivors



	Ipilimumab (*N* = 399)	Placebo (*N* = 400)
OS (mo), median (95% CI)	11.0 (9.5–12.5)	10.0 (8.4–11.2)
Piecewise HR (95% CI)	0–5 mo, 1.49 (1.12–1.99) 5–12 mo, 0.66 (0.51–0.86) Beyond 12 mo, 0.66 (0.52–0.84)	

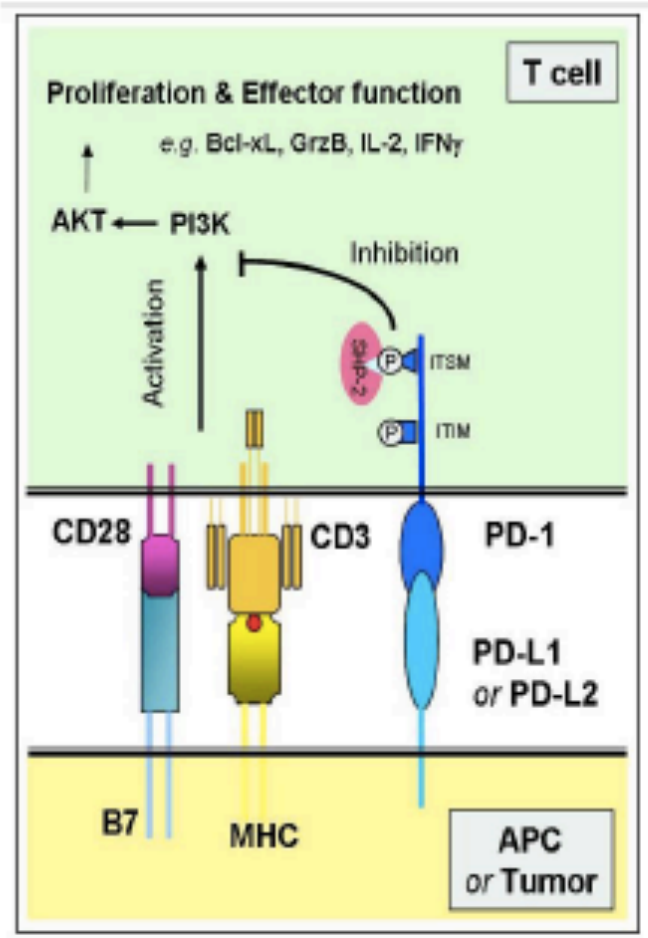
Fig. 1 – Overall survival. CI = confidence interval; HR = hazard ratio; OS = overall survival.

Additional follow-up of 2.4 years since the primary analysis

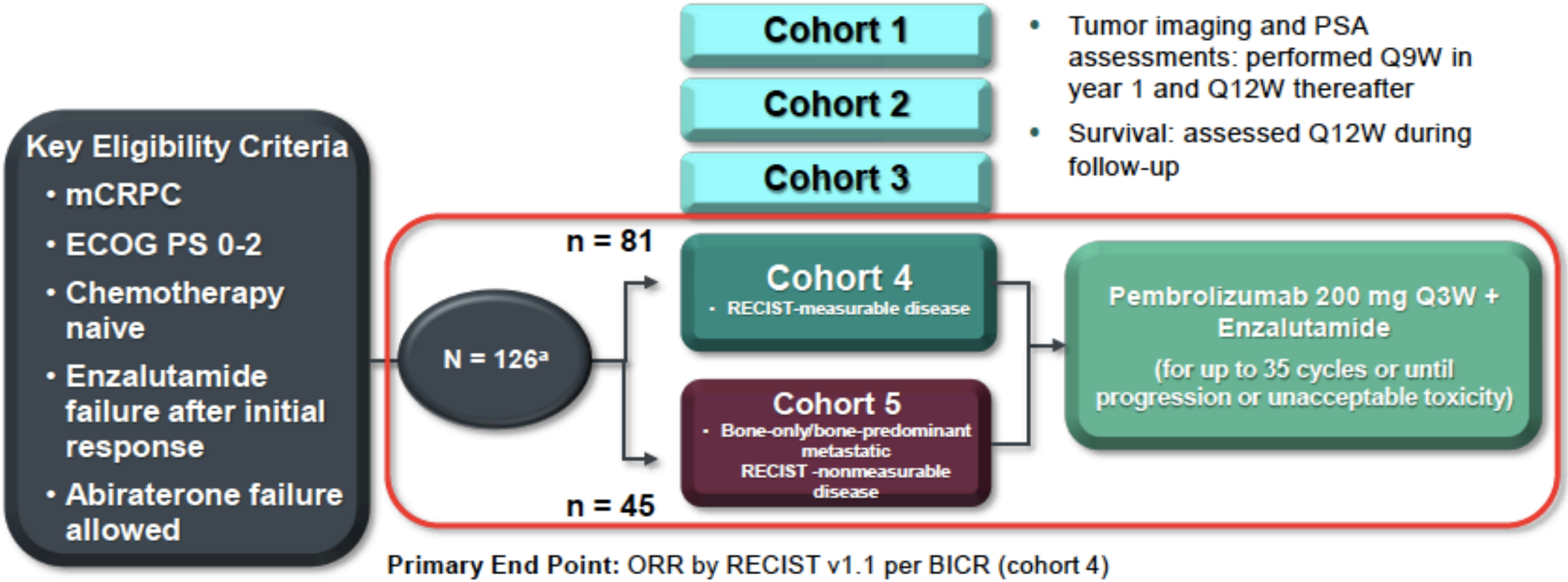
Fizazi K et al, Eur Urol. 2020 Dec;78(6):822-830

The PD-1 Receptor-Ligand Interaction is Important for Immune Tolerance

- **PD-1** is a transmembrane receptor expressed **on activated T lymphocytes**
- PD-1 interacts with its ligands (PD-L1/L2; expressed on various cell types) to inhibit activation of T lymphocytes and down-regulate unwanted or excessive immune responses
- **Human cancers expressing the PD-L1/L2 ligands can 'hijack' the PD-1 pathway**, resulting in **suppression of anti-tumor immune response** and promotion of immune tolerance
- **Blockade of the PD-1 receptor-ligand interaction can reactivate anti-tumor immunity**

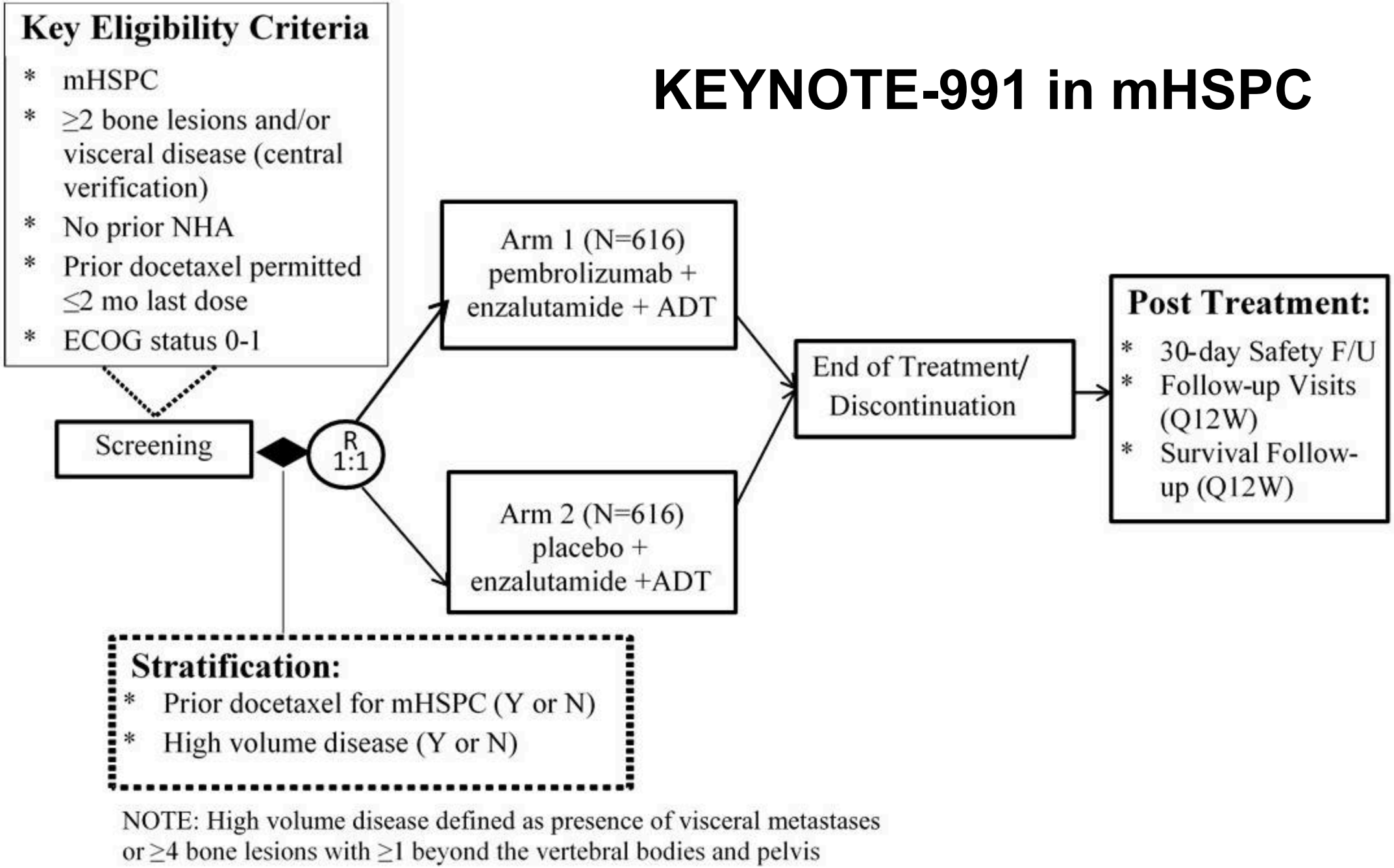


KEYNOTE-199 Study Design



Primary End Point: ORR by RECIST v1.1 per BICR (cohort 4)
Secondary End Points: DCR (RECIST v1.1), rPFS (PCWG3-modified RECIST v1.1), PSA response rate, OS, and safety (cohorts 4 and 5); DOR (RECIST v1.1, cohort 4)

KEYNOTE-991 in mHSPC



NOTE: High volume disease defined as presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis

Magic 8

Biochemical Relapse or mHSPC
PSADT < 12 mos, low volume < 4 bone mets, LN mets < 3 cm

Arm A:
Nivolumab 480mg IV every 4 weeks, followed by Nivolumab 480mg IV + Degarelix (240mg loading dose, then 80mg) SQ every 4 weeks.

Arm B:
Nivolumab 480mg IV every 4 weeks + BMS-986253 2400mg IV every 2 weeks followed by Nivolumab 480mg IV + BMS-986253 2400mg IV every 2 weeks + Degarelix (240mg loading dose, then 80mg) SQ every 4 weeks.

BMS-986253 2400mg is Anti IL-8

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- Prostate Cancer Disparities: AA P-1000 and DoD

Neuroendocrine Prostate Cancer (NEPC): Unmet Need

- NEPC is an aggressive histologic variant of prostate cancer that may arise de novo or as a mechanism of treatment resistance
- Prognosis of NEPC is poor owing to its aggressive and heterogeneous clinical features
- Median survival for metastatic NEPC is less than one year
- There are no approved therapies
- Novel treatments for NEPC is a dire unmet medical need

Neuroendocrine Prostate Cancer (NEPC)

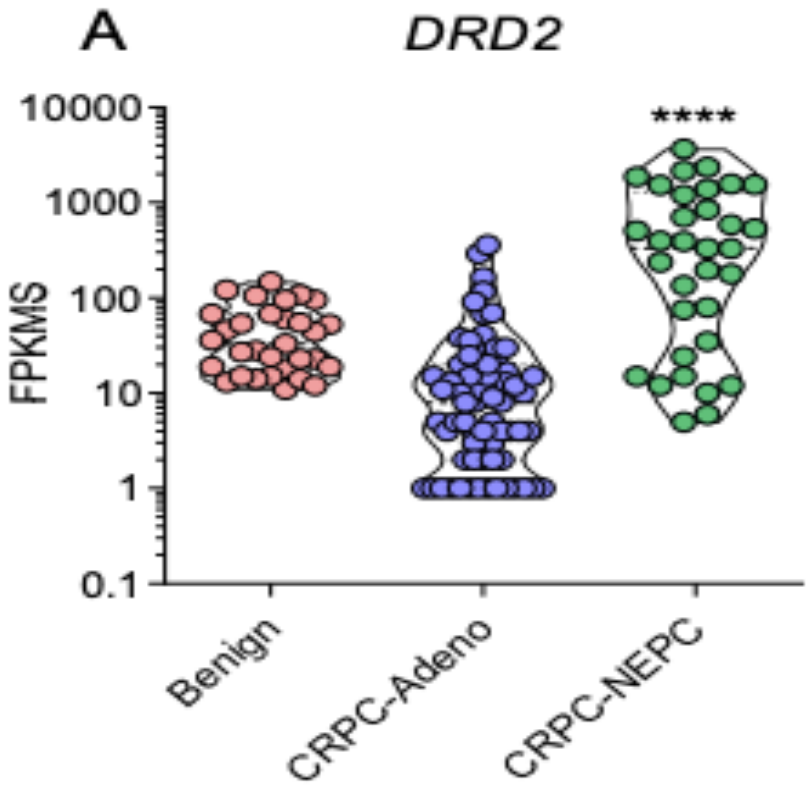
- NEPC evolves from AdenoCa and CRPC through lineage conversion to the neuroendocrine lineage and loss of AR signaling dependence
- Genetic and/or dysregulation of at least one epigenetic modifier histone methyl transferase enhancer of zeste 2 (EZH2)
- Alterations in RB1, Tp53, and/or PTEN and N-MYC over-expression are more frequent in NEPC than in CRPC

NEPC Patient derived organoids

- Lack of *ex vivo* prostate cancer models
- To address this unmet need, we have developed protocols for growing tumor organoids from metastatic NEPC patients
- Patient-derived NEPC organoids recapitulate patient response to targeted therapies and have helped identify novel therapeutic targets, e.g. EZH2

1. Puca et al, Nat Commun. 2018 Jun 19;9(1):2404
2. Mosquera et al, Nature Materials, submitted

WCMC: Dopamine Receptor D2 (DRD2) is upregulated in NEPC patients compared to CRPC patients and benign tumor



Integrated mRNA analysis NEPC patients among the transcriptomic cohort expressed a significant 27-fold higher expression of DRD2 relative to CRPC-Adeno patients

No. of pts.	31	74	35

Mosquera et al, Nature Materials, submitted

Molecular Basis of Lineage Plasticity and AR-Independent Prostate Cancer: Study Design

- **Sample Size:** 100
- **Enrollment:** This study will plan to enroll up to 100 patients. There are retrospective samples from 80 patients and we plan to collect approximately 100 prospective samples in a 5 year period.
- **Study Population:** Patients with suspected Metastatic Neuroendocrine Prostate Cancer (NEPC)
- **Enrollment Period:** 5 years

Exploratory Objectives (1)

- **Molecular assays will be performed on archival or fresh frozen material and blood, and will include but not limited to:**
- 1) DNA analysis of DNA extracted from frozen or paraffin embedded tumor tissue, ctDNA, circulating tumor cells (CTCs), and normal cells (control).
- For prospective pts, normal peripheral blood leukocytes, buccal swab, and/or surrounding non-cancerous tissue obtained in the biopsy specimen will serve as control. For retrospective subjects, control specimen may be limited to the noncancerous portion of tissue section if no peripheral blood or buccal swab are available.
- 2) Expression profile analysis of RNA extracted from fresh frozen or paraffin embedded tumor tissue or circulating tumor cells utilizing next generation RNA sequencing platforms as well as tissue microarrays.
- 3) Molecular analysis of tissue and/or circulating tumor cells for protein expression; cell free DNA (cfDNA) and/or RNA

Exploratory Objectives (2)

- 4) Single cell sequencing of tumor and/or stroma cells
- 5) Organoid growth when fresh tissue is available for patient-derived tumor organoid development
- 6) Methylation assays on tissue and plasma biospecimens
- 7) Mass cytometry and spatial transcriptomics analysis of tissue
- **The assocation of any molecular analysis may be evaluated for an association with overall survival and clinical parameters. All samples will be de-identified**

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VOLUME 33 · NUMBER 10 · APRIL 1 2015

JOURNAL OF CLINICAL ONCOLOGY

COMMENTS AND CONTROVERSIES

Disparities in Castration-Resistant Prostate Cancer Trials

Daniel E. Spratt and Joseph R. Osborne, *Memorial Sloan Kettering Cancer Center, New York, NY*

Table 1. Summary of Enrollment of Black Men Onto CRPC Trials

Enrollment	Sipuleucel-T	Radium-223 Chloride	Enzalutamide (pre-chemo)	Enzalutamide (post-chemo)	Abiraterone (pre-chemo)	Abiraterone (post-chemo)	Cabazitaxel	All Patients With CRPC in RCTs	Expected Black Enrollment*
Total patients	512	809	1,717	1,199	1,195	1,088	755	7,275	
Random assignment	2:1	2:1	1:1	2:1	2:1	1:1	1:1	—	
Percent black	5.8	2.0	2.0	3.9	3.6	2.8	5.3	3.3	15.8
No. of black patients	30	16	34	47	43	30	40	240	1,149
No. of black patients receiving trial drug	23	11	21	31	29	15	20	150	673

Abbreviations: chemo, chemotherapy; CRPC, castration-resistant prostate cancer; NCI, National Cancer Institute; RCT, randomized controlled trial.
*Based on (1) conservative NCI enrollment data that 66% of the available black population enrolls onto NCI clinical trials; (2) the US population is approximately 12% black; (3) there is a greater than two-fold increase in the incidence of lethal prostate cancer in black men.[1a,9]

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Weill Cornell Medicine

NewYork-Presbyterian

Prostate Cancer Disparites

The “Afro-NY” Prostate Cancer Program:

A multi-institutional and multi-disciplinary project

The “Afro-NY” Prostate Cancer Program: A multi-institutional and multi-disciplinary project

Novel complex structural variants and epigenetic alterations link the genomes of African ancestry prostate cancer with outcome disparity

DOD - W81XWH-20-PCRP-HDRA (PI: Mosquera)
Co-I: **Sternberg**, Elemento, Nanus, Imielinski, Nauseef, Davis, Martin, Robinson, Chen

Molecular links between ancestry and outcome disparity in prostate cancer patients across the African diaspora in New York City

New York Genome Center P1000: PIs: Mosquera, **Sternberg**, Imielinski, Elemento,, Polak, Davis

“Afro-NY” Prostate Cancer Program

NewYork-Presbyterian

Weill Cornell Medicine

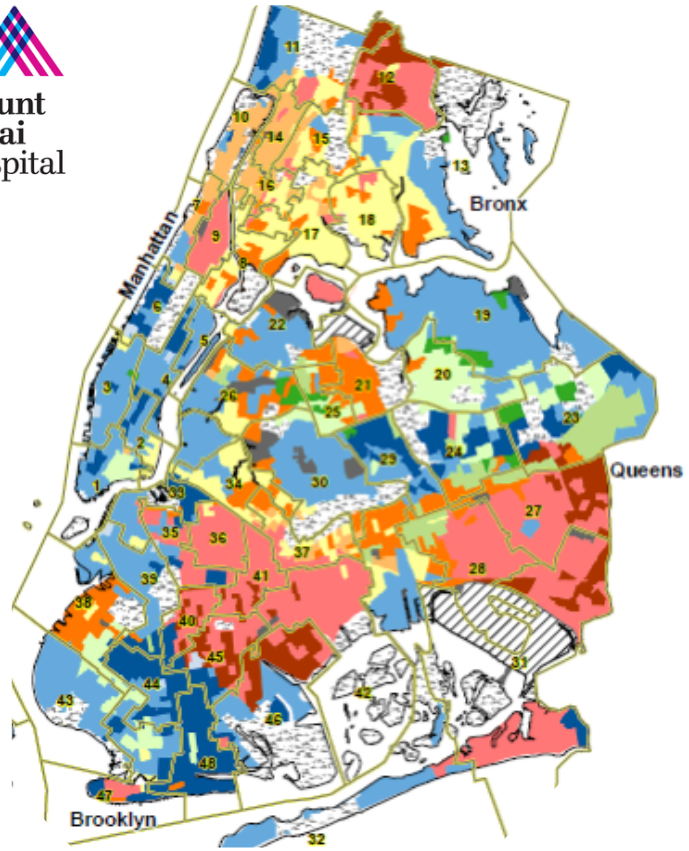
Weill Cornell Medicine
Caryl and Israel Englander
Institute for Precision Medicine

Columbia University Medical Center

Mount Sinai Hospital

NYU

NEW YORK GENOME CENTER



NewYork-Presbyterian
Queens

NewYork-Presbyterian
Brooklyn Methodist Hospital

North Carolina-Louisiana PCaP Prostate Cancer Project

ROSWELL PARK COMPREHENSIVE CANCER CENTER

Department of Defense - W81XWH-20-PCRP-HDRA *(Mosquera)*
New York Genome Center P1000 *(Mosquera, Sternberg, Imielinski, Elemento,, Polak, Davis)*

Goals and Deliverables

- The overarching goal is to define the genomic (WGS/RNA-seq) landscape and to bring AA prostate cancer to a whole genome-based standard of care

- Our preliminary analyses of simple and complex structural variants (SVs) reveal potentially clinically significant SV-mediated sequelae (HRD), which underscore the value of WGS, including as a hypothesis generating approach to validate findings using orthogonal methods both *in silico* and in pre-clinical *in vitro* models

- It will require larger cohorts of both localized and metastatic advanced disease to further uncover genomic biological differences underlying incidence and outcome disparities, not only to increase analytical power. *Recruitment of AA men to these studies will also expand genomic investigations in the AA community, increase ready access to clinical trials, and help deliver precision care*

Goals and Deliverables

- Sequencing and associated metadata will be accessible after 18-month embargo
- Through this program we will generate “Afro-NY”, the most comprehensive Whole Genome Sequencing (WGS) and RNA-sequencing (RNA-seq) profiled sample set of AA prostate cancer patients to date, spanning ~150 AA prostate cancer cases
- A high-quality genomic resource with quantified ancestry, genetic alterations, and mutational signatures across the study cohort

Designing the future Paradigm of Prostate Cancer

- Approximately 90% of mCRPC harbor clinically actionable molecular alterations
- Molecular testing is recommended for all metastatic or high risk patients, Family history
- Molecular classification will guide future treatments

How Precision Medicine and Novel Prostate Cancer Treatments Can Benefit You

- Precision Medicine: Profound trial, Hopkins Trial
- Novel hormonal Rx: M0 CRPC - treating earlier is better PROSPER, SPARTAN, ARAMIS
- AR Degraders: Arvinas Trial
- Immunotherapy Trials: Enzalutamide +Pembrolizumab and Magic 8 (Nivolumab + anti IL-8)
- NEPC (novel approaches are needed)
- Prostate Cancer Disparities: (we will continue to study and change this paradigm)