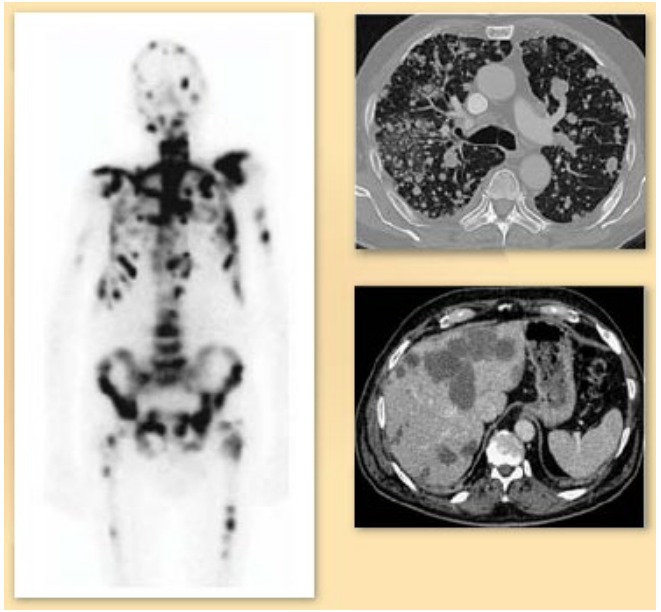
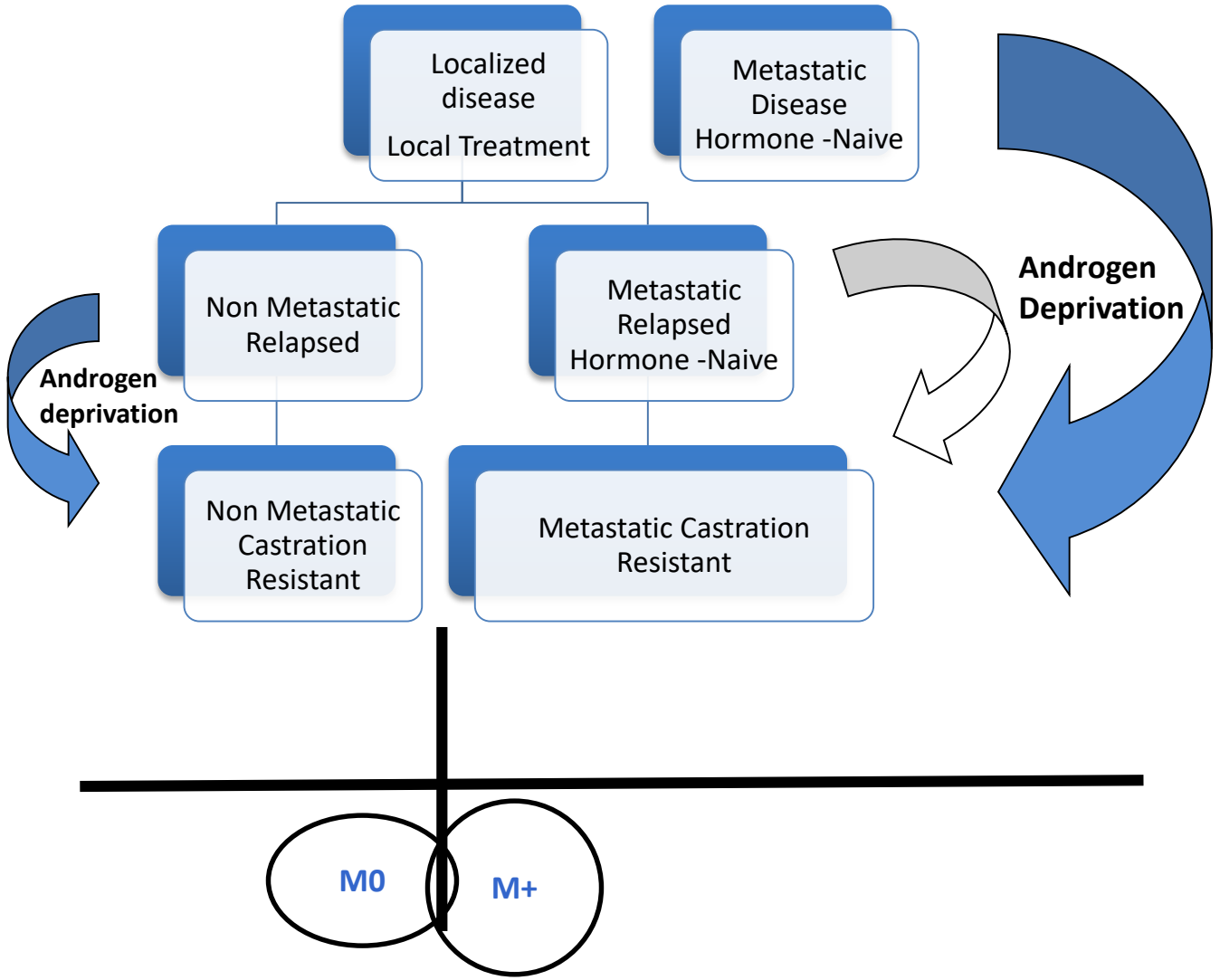
New and Developing Treatment Approaches for Patients with Non-Localized Prostate Cancer

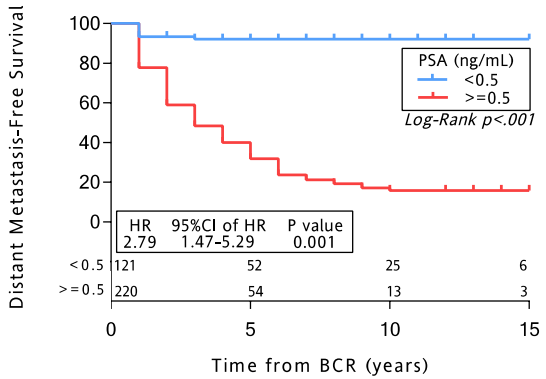


The prostate cancer clinical paradigms in the 21st Century



M0 Prostate Cancer

- Biochemical Recurrence (hormone naïve)
  - Natural history is very long
  - PSADT < 9 months → consider treatment (ADT)



Markowski et al, CGUC, 2019 in press

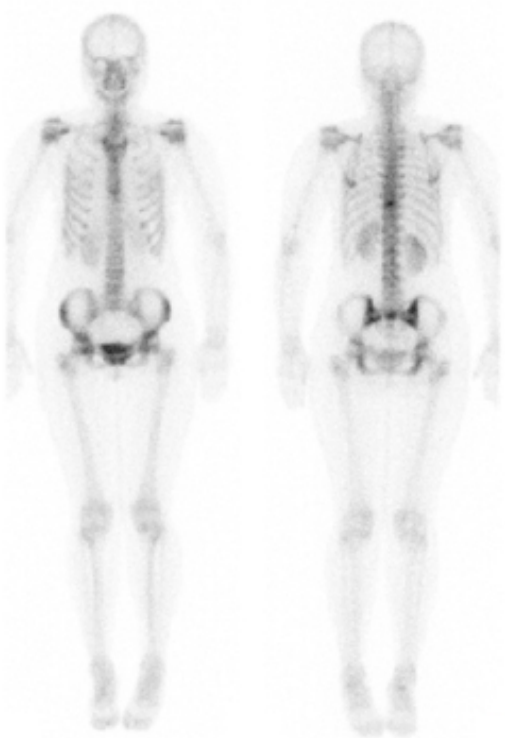
- Non-Metastatic Castration Resistant PCa
  - Apalutamide, enzalutamide, darolutamide (PSADT < 10 mths)
  - ?Does early treatment improve OS from time of diagnosis

JHU and CPDR Experience measured from time of RRP (GS- Global Survival)

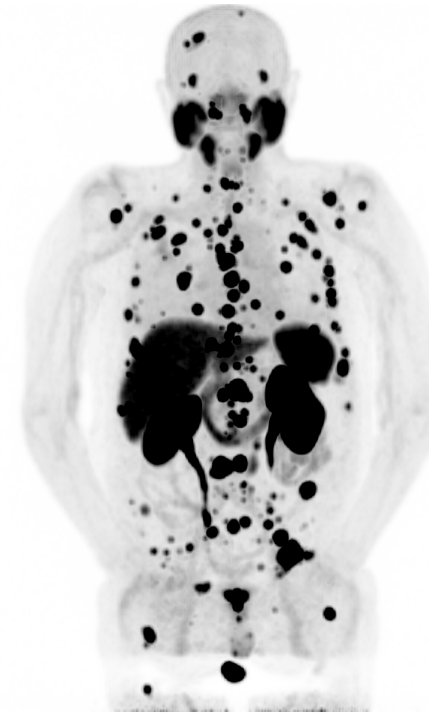
	All	≤ 6 months	≤ 10 months
# who developed M1, n(%)	595 (20%)	198 (45%)	309 (38%)
Median MFS (all) (95% CI)	Not reached	12 years (8-15 years)	16 (15-21 years)
Median MFS (M+ only) (95% CI)	6 years (6-7 years)	3 years (3-4 years)	4 (4-5 years)
Median Survival (95% CI)	21 (20-22 years)	14 years (12-17 years)	17 years (15 – 18 years)

Marshall et al, ESMO 2019

M0 is the New M1



Bone scan – M0 disease, BCR

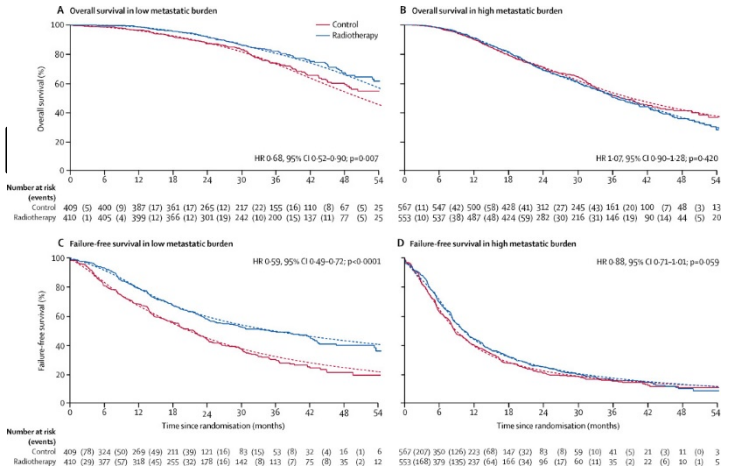


^{18}F-DCFPyL
PSMA-PET
M1 disease, mHNPC

What's new in mHSPC

- "more is better" – kitchen sink approach
  - Docetaxel (CHAARTED), volume status may not matter
  - Abiraterone (STAMPEDE, LATITUDE)
  - Enzalutamide/apalutamide (ENZAMET, TITAN)

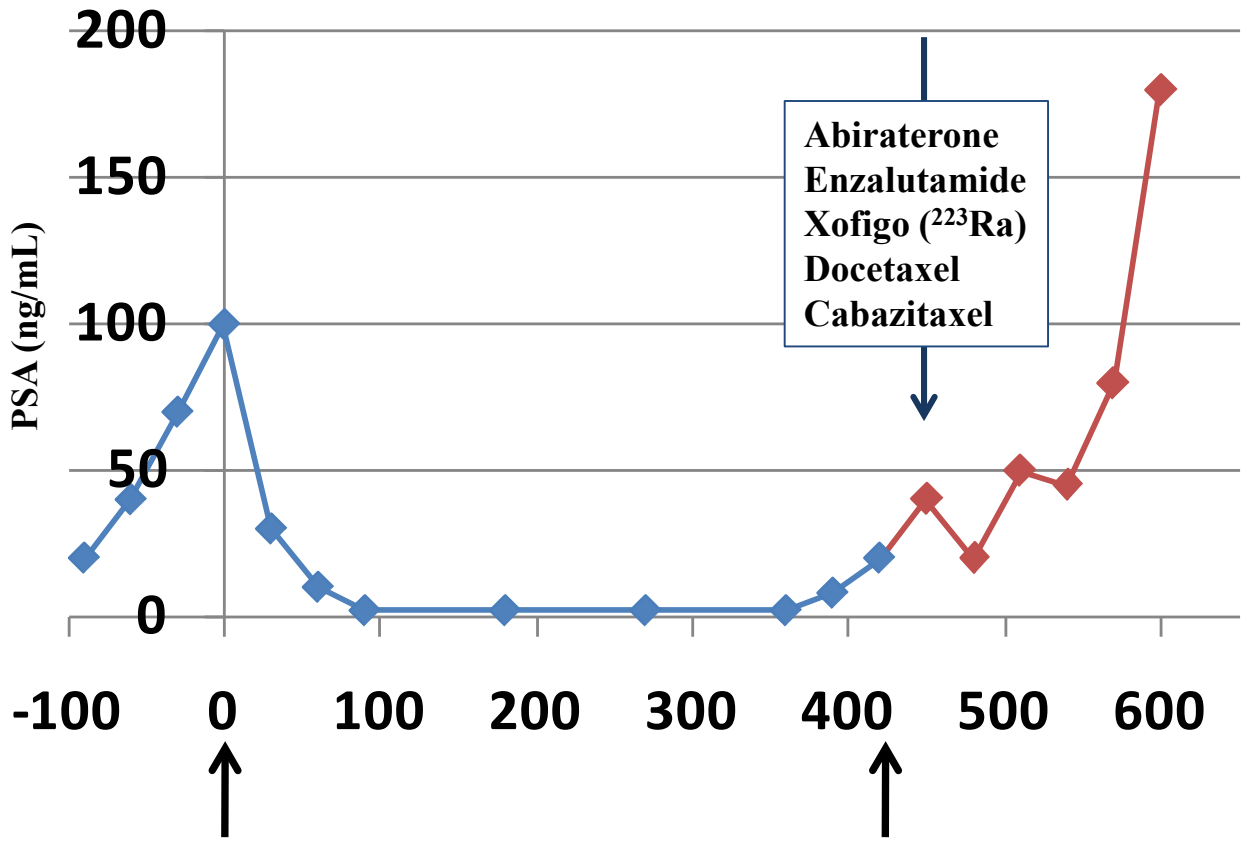
- Radiation to primary?
  - Maybe in low volume disease (STAMPE

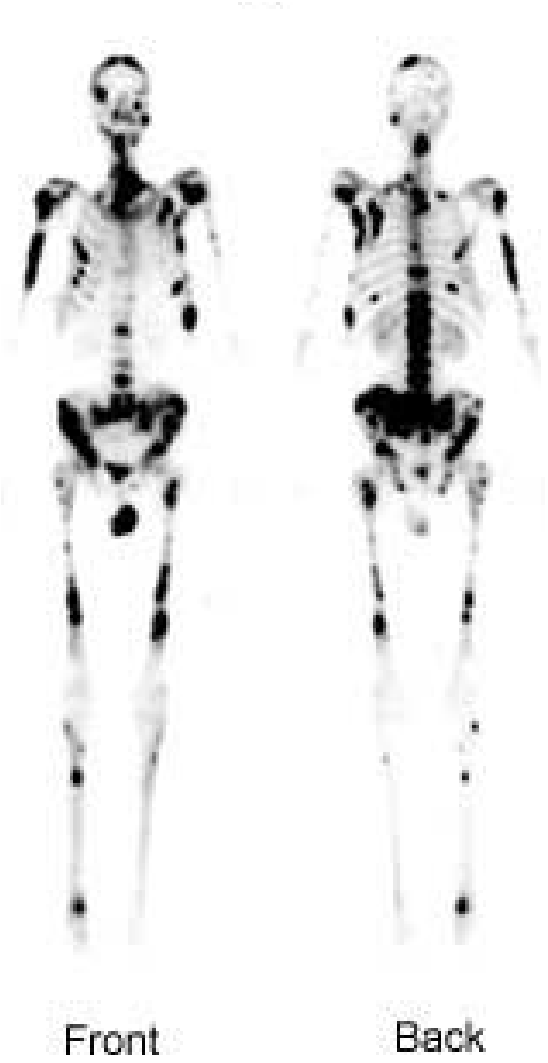


Parker et al, Lancet Oncology, 2018

Future Treatments for mCRPC Prostate Cancer

Metastatic Prostate Cancer Remains an Incurable Disease





75 years of Androgen Ablation

1940s-60s

Orchiectomy
Diethylstilbesterol
Adrenalectomy
Hypophysectomy

1970s-90s

LHRH agonists
Goserelin
Triptorelin
Buserelin
Histrelin
Nafarelin
Leuprolide…

LHRH antagonists
Degarelix
Abarelix

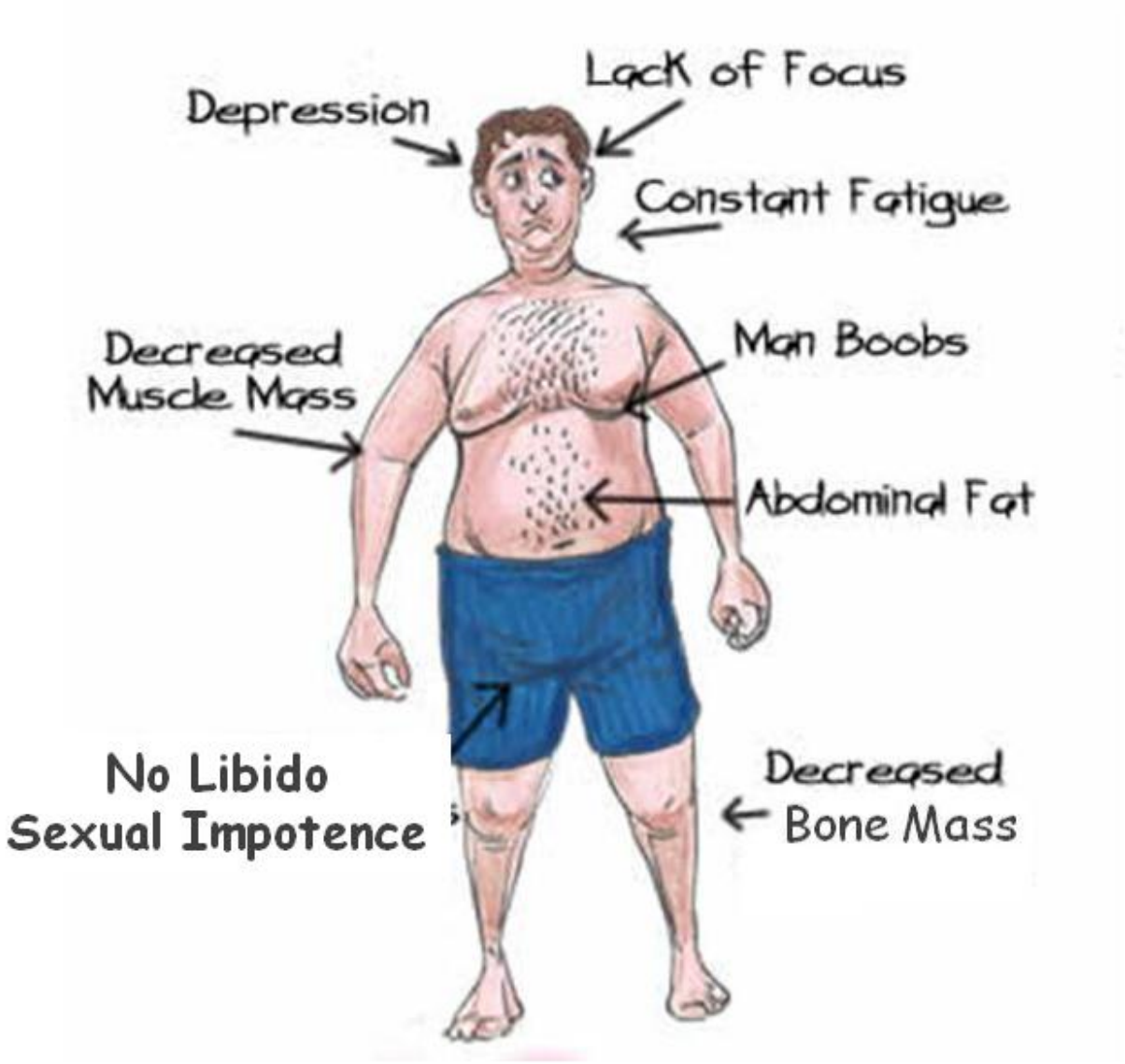
Antiandrogens
Cyproterone Acetate
Flutamide
Bicalutamide
Nilutamide

Adrenal Poisons
Aminoglutethimide
Ketoconazole

21st Century

Abiraterone
Enzalutamide
Apalutamide
ODM-201

Androgen Deprivation Therapy Side Effects



Two Principles in Endocrine Therapy of Cancers: Hormone Deprival and Hormone Interference[1]

SUMMARY

Hormones, or synthetic substances exerting physiologic effects similar thereto, are of crucial significance for growth of 7 hormone-dependent cancers of man and the animals. Two opposite sorts of change of the hormonal status can induce regression of such cancers: (*a*) deprivation of essential hormones; (*b*) hormone interference with large amounts of critical compounds.

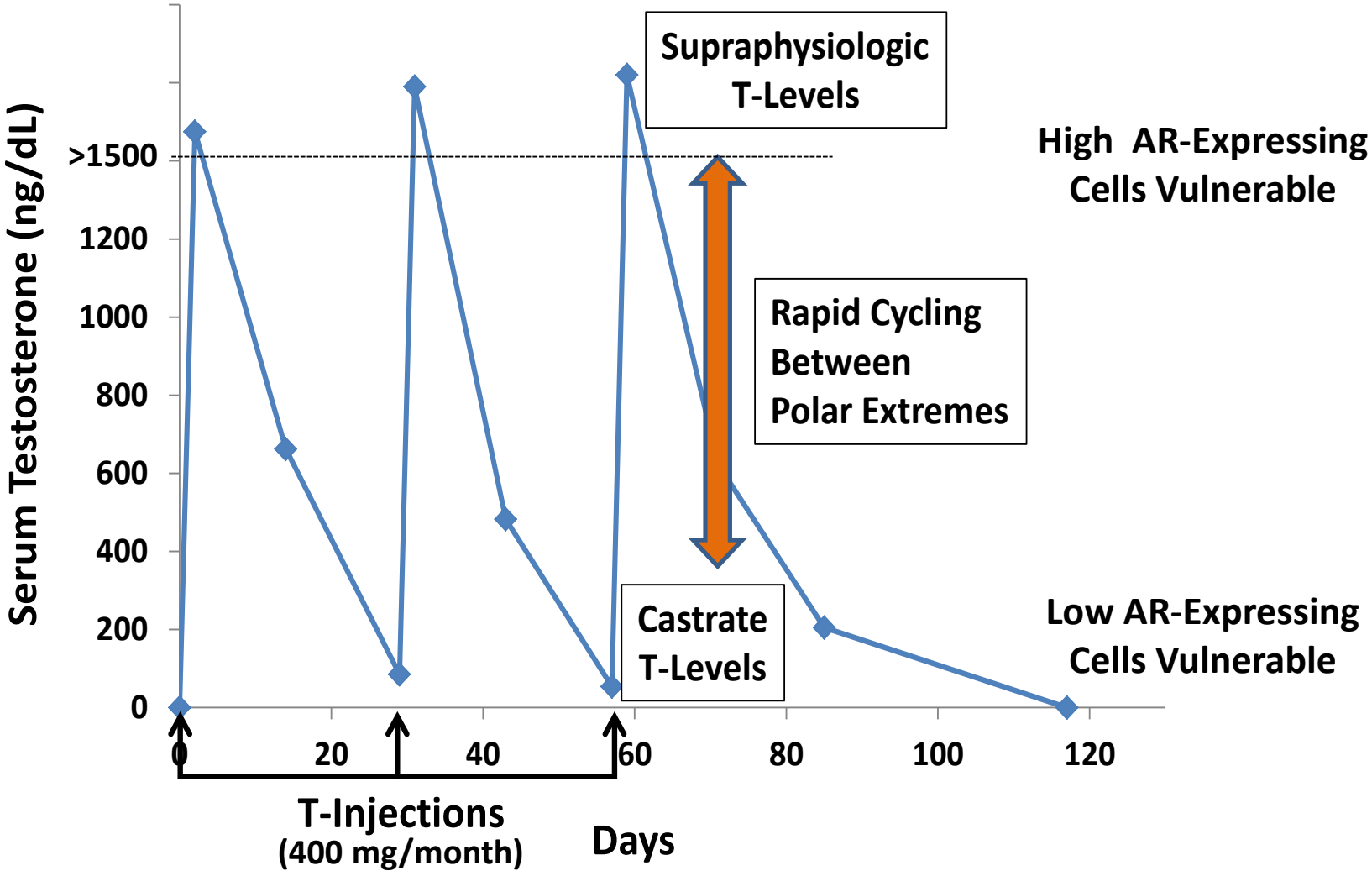
Hypothesis:

- **Men with Castrate Resistant Prostate Cancer could respond to rapid cycling between polar extremes of supraphysiologic and castrate testosterone levels [Bipolar Androgen Therapy (BAT)].**

- **Rapid cycling disrupts adaptive autoregulation of AR.**

- **Adaptive downregulation of AR expression may re-sensitize CRPC to androgen ablative therapies**

"Bipolar Androgen Therapy"

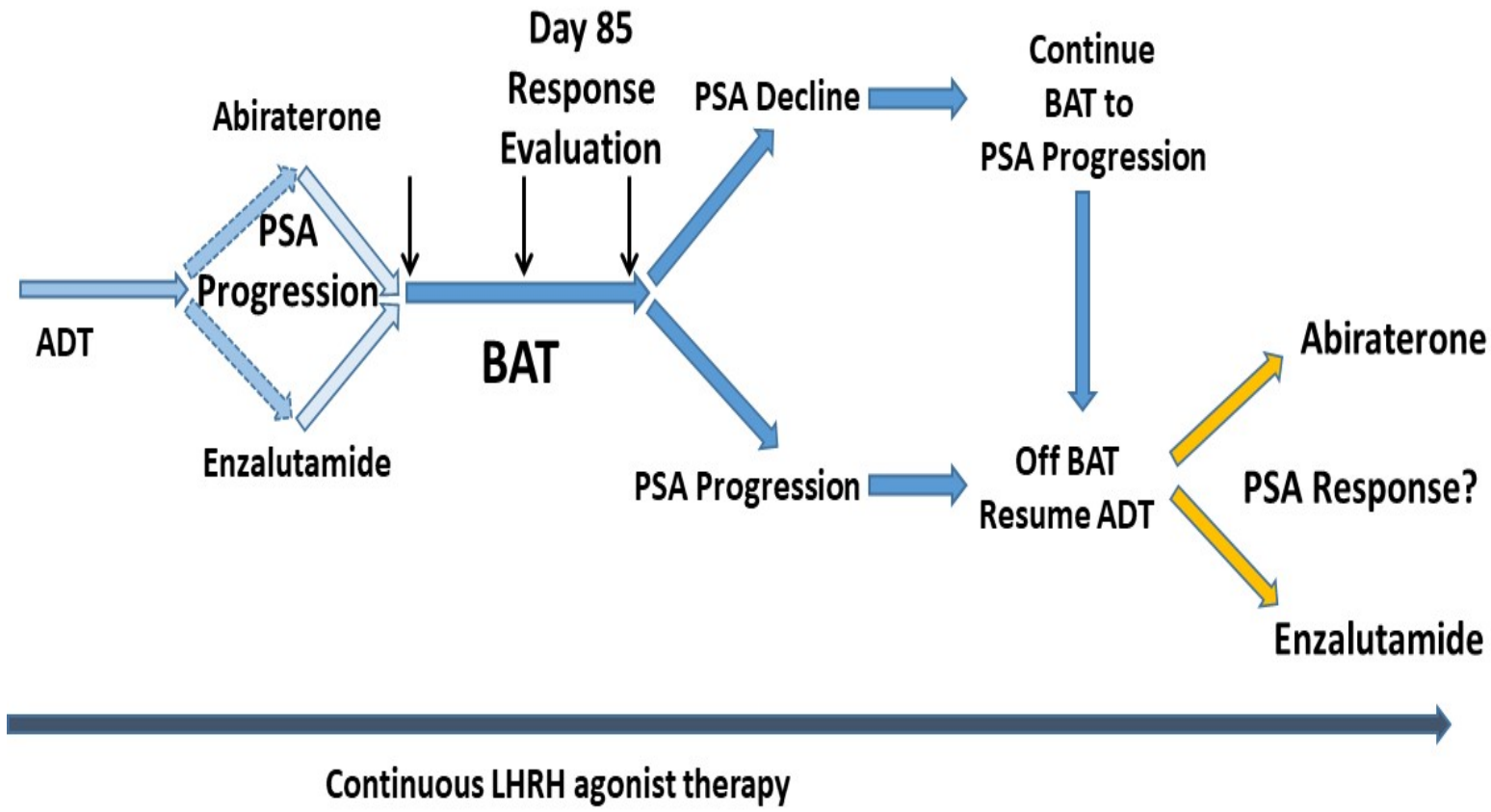


Pilot Study Response Summary

- **8 of 14 men had some PSA decline**
- **30% had >50% PSA decline**
- **Median Response was 248 Days**
- **4 men received ≥ 12 cycles of T**
- **50% Objective Response by RECIST**
- **10/10 patients had some PSA decline on abiraterone or anti-androgens post-BAT**

Subject #	Cycles (N)	Max PSA change relative to baseline %	RECIST Response
15	9	-39	**PR**
8	3	-46	SD
6	13	-48	**PR**
3	6	-60	SD
9	18	-78	NA
4	15	-86	**PR**
13	16	-97	**PR**
16	6	-98	**CR**

RE-sensitizing with Supraphysiologic Testosterone to Overcome REsistance (The RESTORE Study)



BAT Pre-Treatment	Total	PSA50	%	95% CI[1]	Any PSA Response[2]	%
Two cohorts of the trial						
Last Drug Enza (Cohort A)	30	9	30.0%	[16.3%, 47.6%]	16	53.3%
Last Drug Abi (Cohort B)	28	5	17.9%	[7.3%, 35.7%]	11	39.3%
Post-hoc analysis						
Combined Cohort A and B	58	14	24.1%	[13.9%, 36.6%]	27	46.6%
Two drugs (Abi-Enza or Enza-Abi)	21	6	28.6%	[13.2%, 50.6%]	12	57.1%
One Drug (Abi or Enza)	37	8	21.6%	[9.8%, 38.2%]	15	40.5%

Post-BAT Rechallenge Response						
Enza	21	15	71.0%			
Abi	19	4	21.0%			

[1]Both Cohorts A and B successfully met the endpoint for PSA50 Response
[2]Any PSA Response denotes any decline in PSA within first 3 cycles of BAT.

BAT Improves Quality of Life Parameters

Domain	p value
SF-36 Instrument	
-Physical Function	0.0468
-Emotional Well Being	0.0197
-Energy-Fatigue	0.0025
-General Health	0.8736
-Pain	0.6526
-Emotional Limits	0.5824
-Physical Health Limits	0.0152
-Social Functioning	0.2735
PANAS-SF Screen Positive Response	0.4977
PANAS-SF Screen Negative Response	0.7756
FACIT Fatigue Scale	0.0026
IIEF	1.7e-08

Paired Wilcoxon test for each QoL metric.
P values were not adjusted for multiple comparison.

Bipolar Androgen Therapy Trials In Metastatic CRPC

- **Pilot [n=14; (One-In-Six Foundation)]**
- **RESTORE [3 cohorts; n=89; (R01)]**
- **TRANSFORMER [randomized vs Enza; n=195; (DOD)]**
- **COMBAT-CRPC (BMS, PCF, DOD)]**
- **Sex-Mismatched BMT + Maintenance BAT (n=3)**
- **BAT in biallelic deletion DNA Repair genes (Anthony Joshua)**
- **BAT + Olaparib (Mike Schweizer)**

<u>In Planning</u>

- **BAT+Radium**
- **BAT in sequence with Enzalutamide**

DNA Repair Deficiency

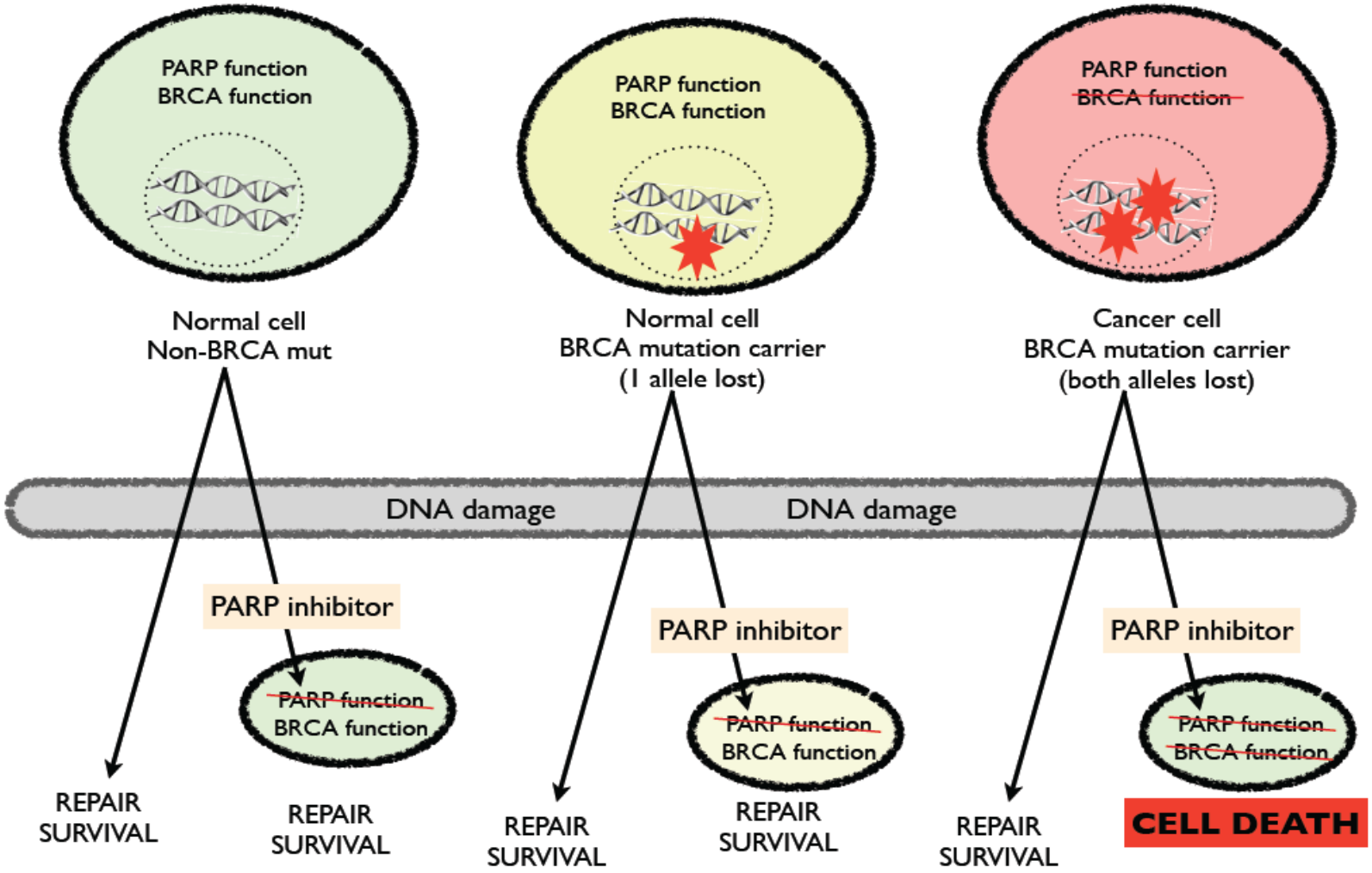
ssDNA Repair Pathways

- ***1. Mismatch repair (MMR)***
  - **Base errors from DNA replication & recombination**
  - ***MSH2, MSH6, MLH1, PMS2***
- **2. Nucleotide excision repair (NER)**
  - **DNA damage from UV light, polycyclic aromatic hydrocarbons**
  - ***XPA–XPG, ERCC1–8, CSA/B, RPA, RAD23A/B***
- ***3. Base excision repair (BER)***
  - **DNA damage from alkylation, oxidation/ROS, deamination**
  - ***PARP1/2/3, POLB, MUTYH, XRCC1, MBD4, NTHL1***

dsDNA Repair Pathways

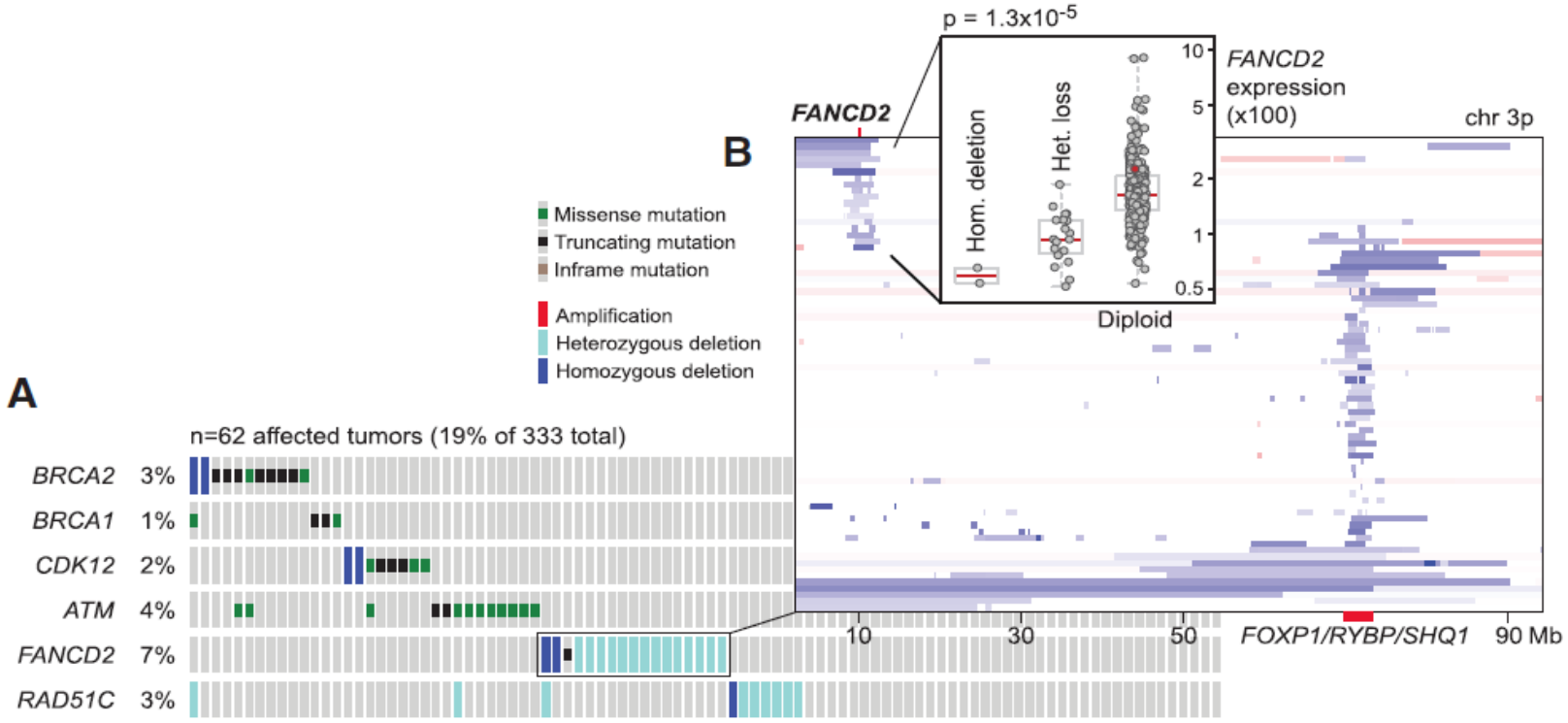
- ***4. Homologous recombination (HR)***
  - DNA damage from ionizing radiation or other dsDNA injury
  - ***BRCA1/2*, *FANC* genes, *ATM*, *PALB2*, *RAD51*, *NBN*, *BLM*, *ATR***
- **5. Non-homologous end joining (NHEJ)**
  - DNA damage from ionizing radiation or other dsDNA injury
  - ***XRCC4/5/6*, *LIG4*, *DCLRE1C*, *PRKDC*, *NHEJ1*, *POLL/M***
- **6. Trans-lesion DNA synthesis (TLS)**
  - Error-prone recovery mechanism when no DNA template
  - ***POLH*, *POLI*, *POLK*, *PCNA*, *REV1/3*** (error-prone DNA polymerases)

Synthetic Lethality



Prevalence of DNA Repair Defects in PCa

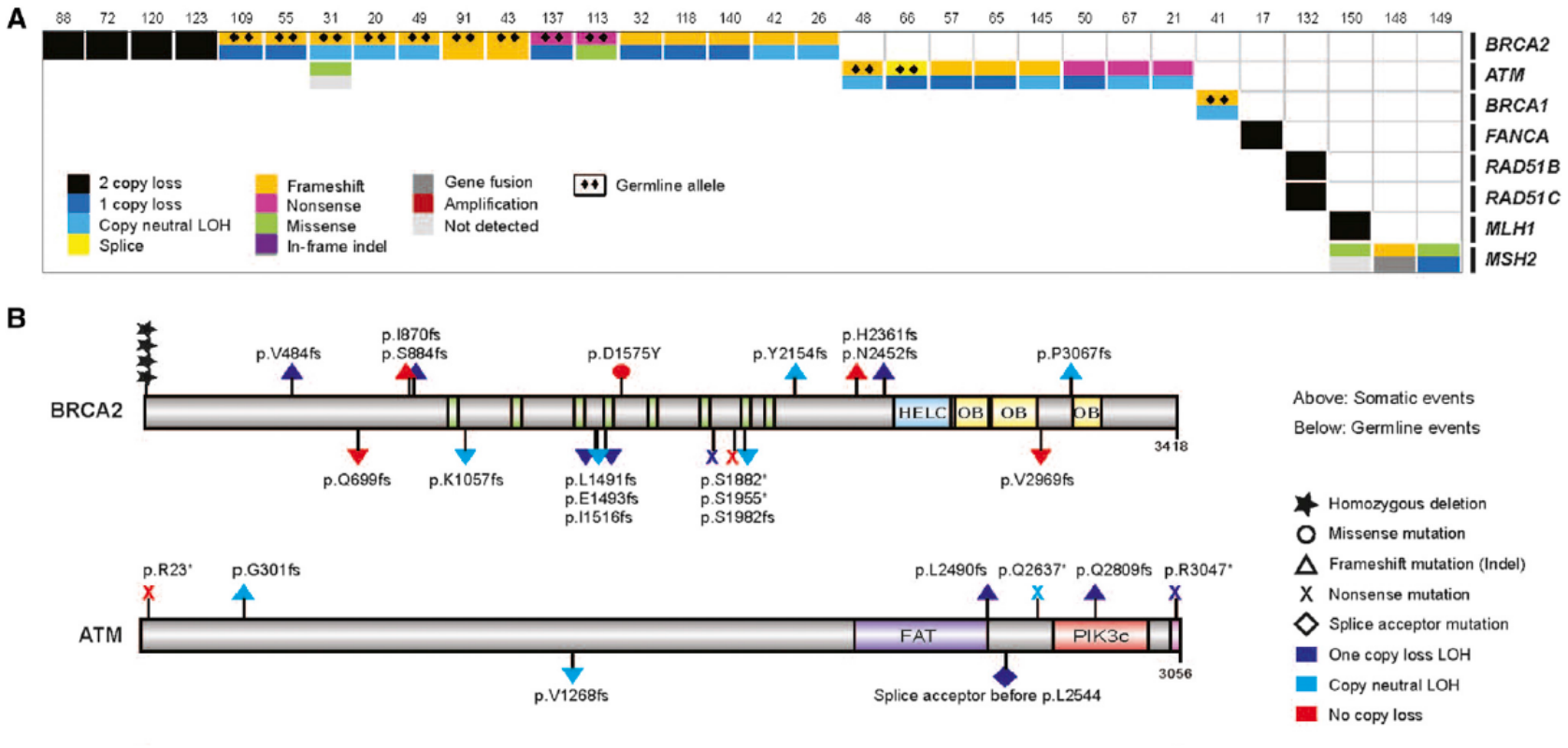
DNA Repair Defects in Localized PC



– **27/333 (8.1%) Tumors had Bi-Allelic inactivation**

Cancer Genome Atlas Network, *CELL* 2015; 163: 1011-25.

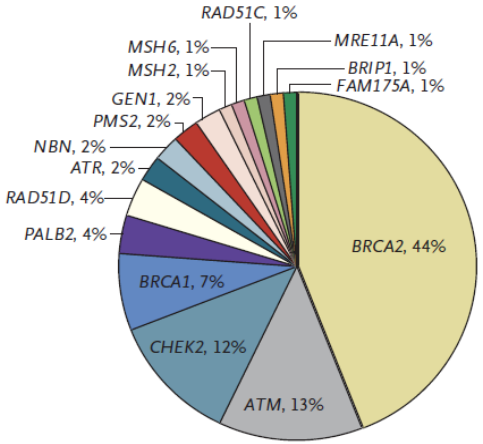
DNA Repair Defects in mCRPC



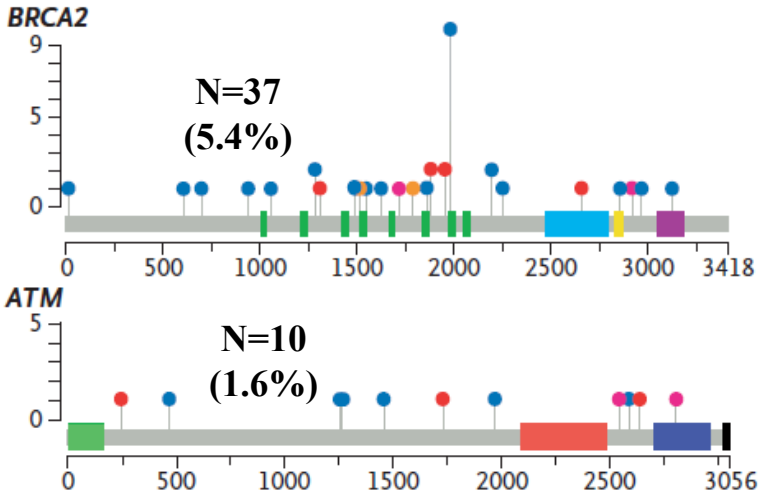
- 32/150 **(21.3%)** had Bi-Allelic DNA repair mutations

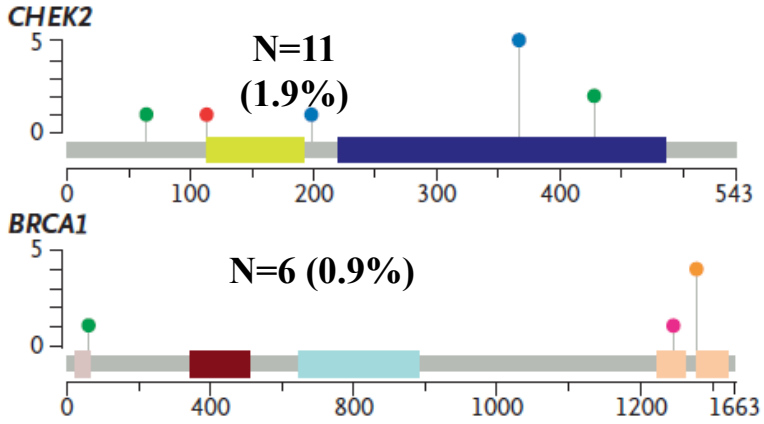
Robinson et al. *CELL* 2015; 161: 1215-28.

Germline DNA Repair Defects



- Germline mutations in 82/692 (**11.8%**) men with met PC
- (and in **4.6%** of 499 men with localized PC)





Pritchard C et al. *NEJM* 2016; 375: 443-53.

TOPARP-A Study in mCRPC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

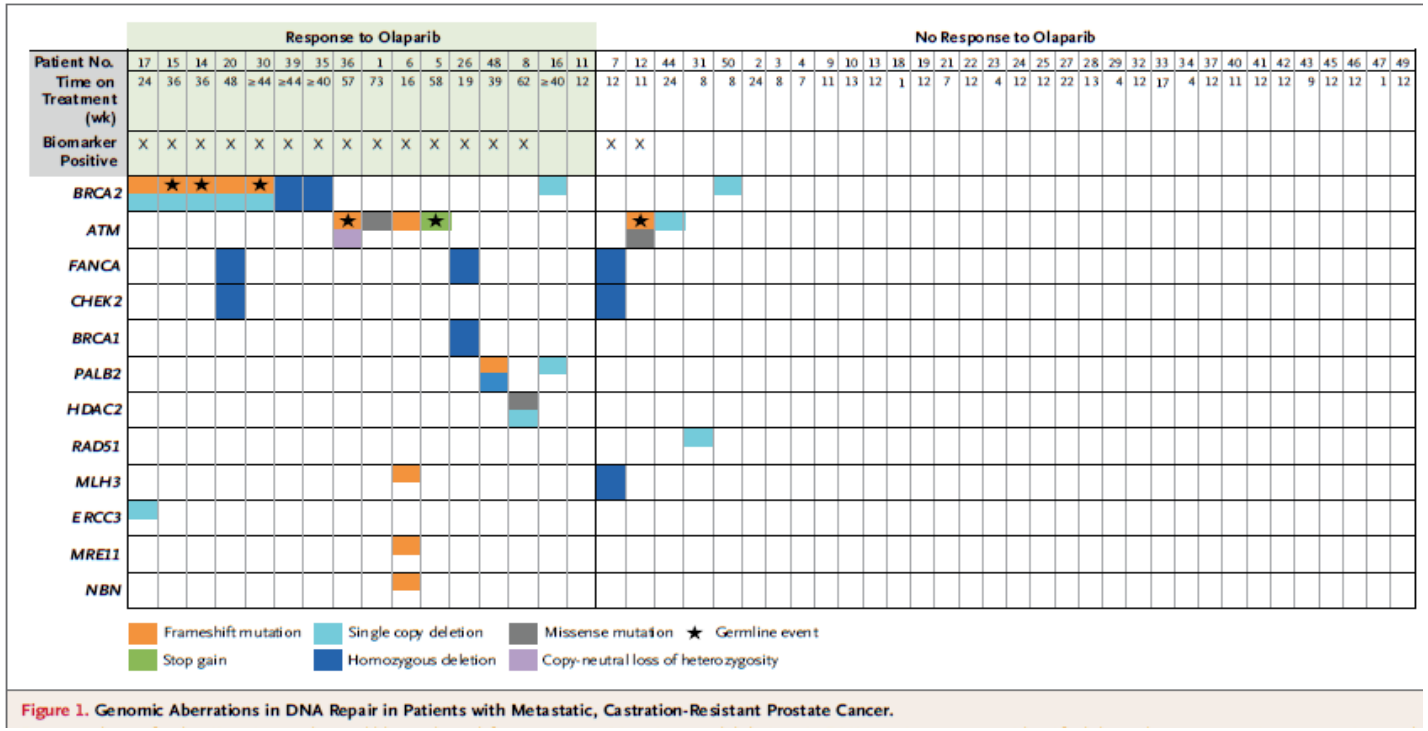
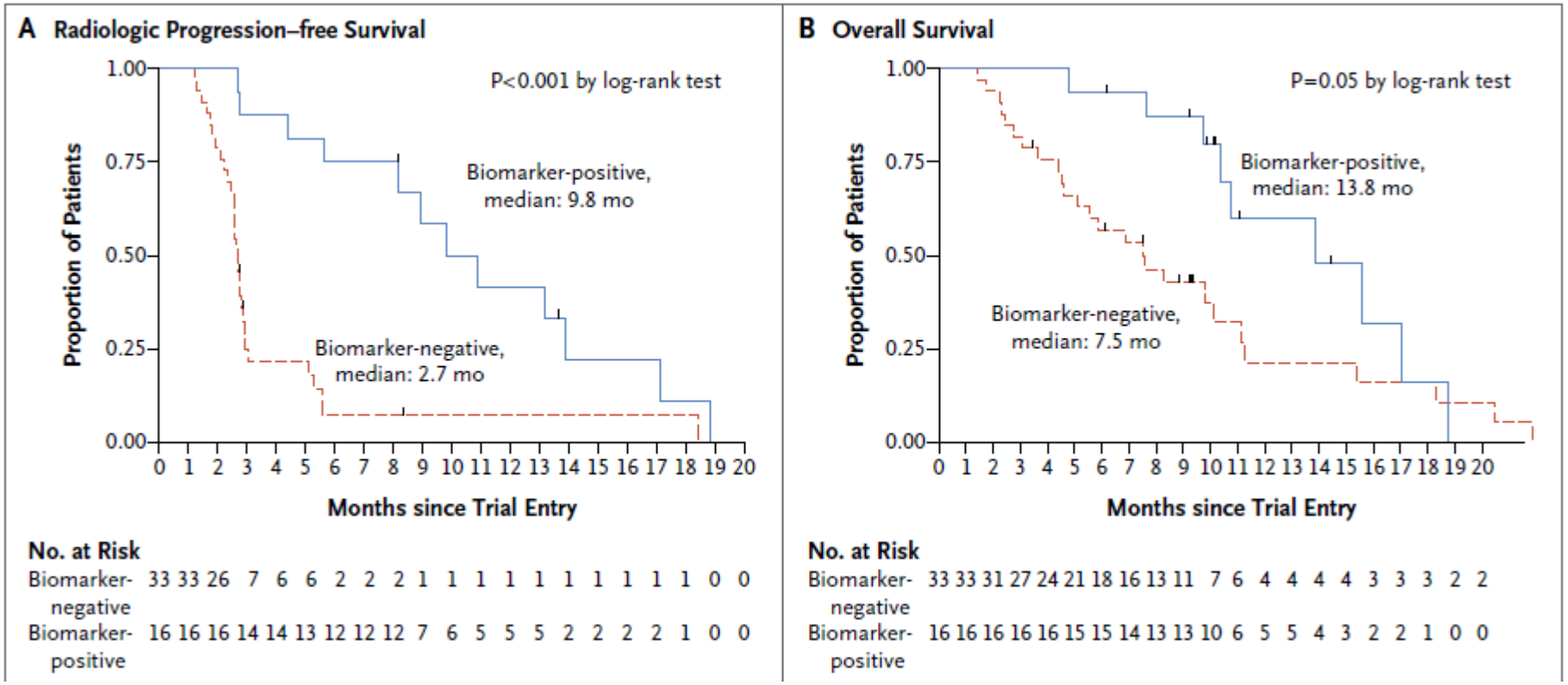


Figure 1. Genomic Aberrations in DNA Repair in Patients with Metastatic, Castration-Resistant Prostate Cancer.

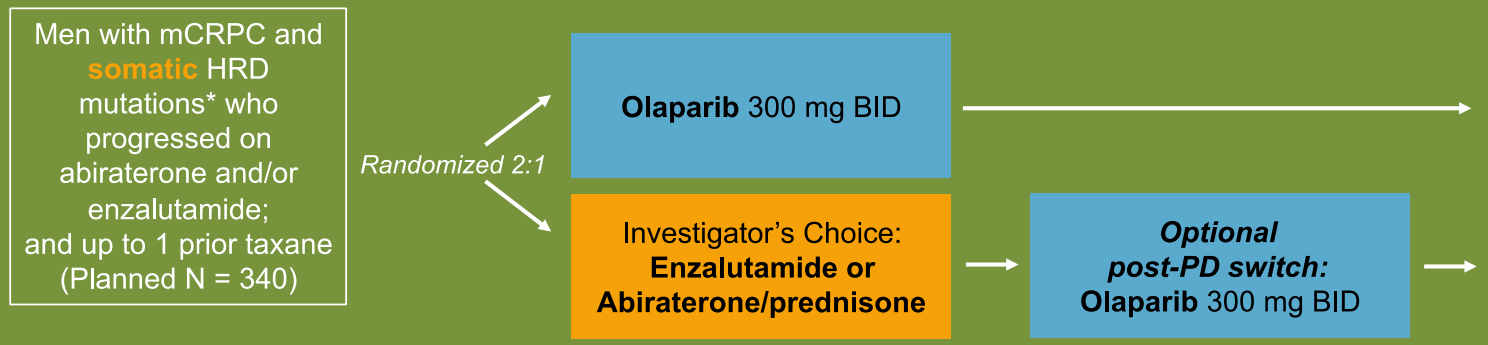
TOPARP-A Study in mCRPC



Mateo J, et al. *NEJM* 2015; 373: 1697-708.

PROfound: Olaparib vs Enza or Abi in mCRPC with somatic HRD mutations

- Open-label, randomized, phase 3 study with rPFS primary endpoint



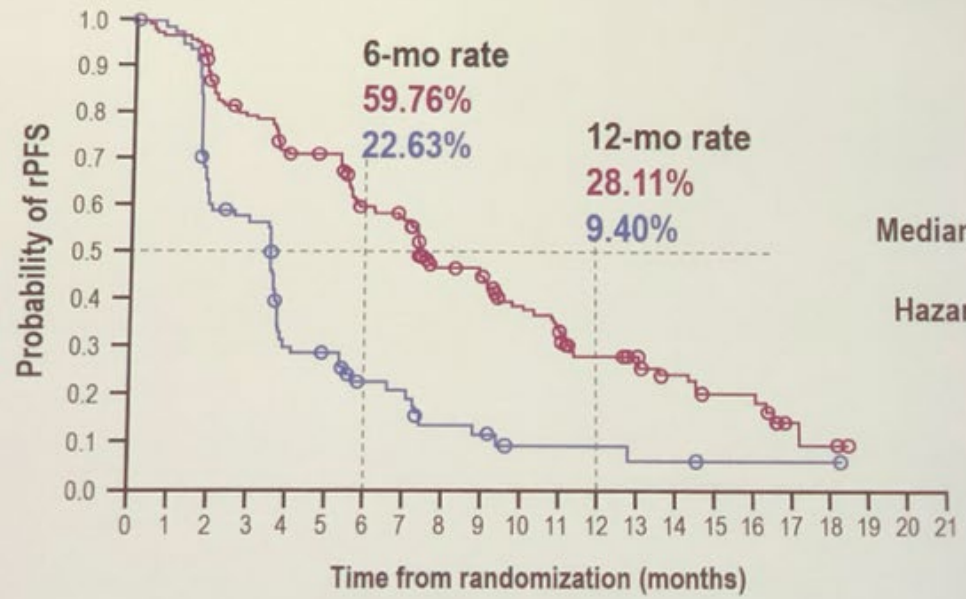
Cohort A: *BRCA1, BRCA2, or ATM*
Cohort B: One of 12 other HRD mutations

- Primary endpoint: rPFS (Cohort A)
- Secondary endpoints: ORR (Cohort A), rPFS (Cohorts A & B), time to pain progression (Cohort A), OS (Cohort A)

ClinicalTrials.gov. NCT02987543

Primary endpoint

rPFS BY BICR IN PATIENTS WITH ALTERATIONS IN *BRCA1*, *BRCA2*, OR *ATM* (COHORT A)



	Olaparib (N=162)	Physician's choice (N=83)
Events (%)	106 (65.4)	68 (81.9)
Median rPFS (months)	7.39	3.55
Hazard ratio (95% CI)	0.34 (0.25, 0.47) *P*<0.0001	

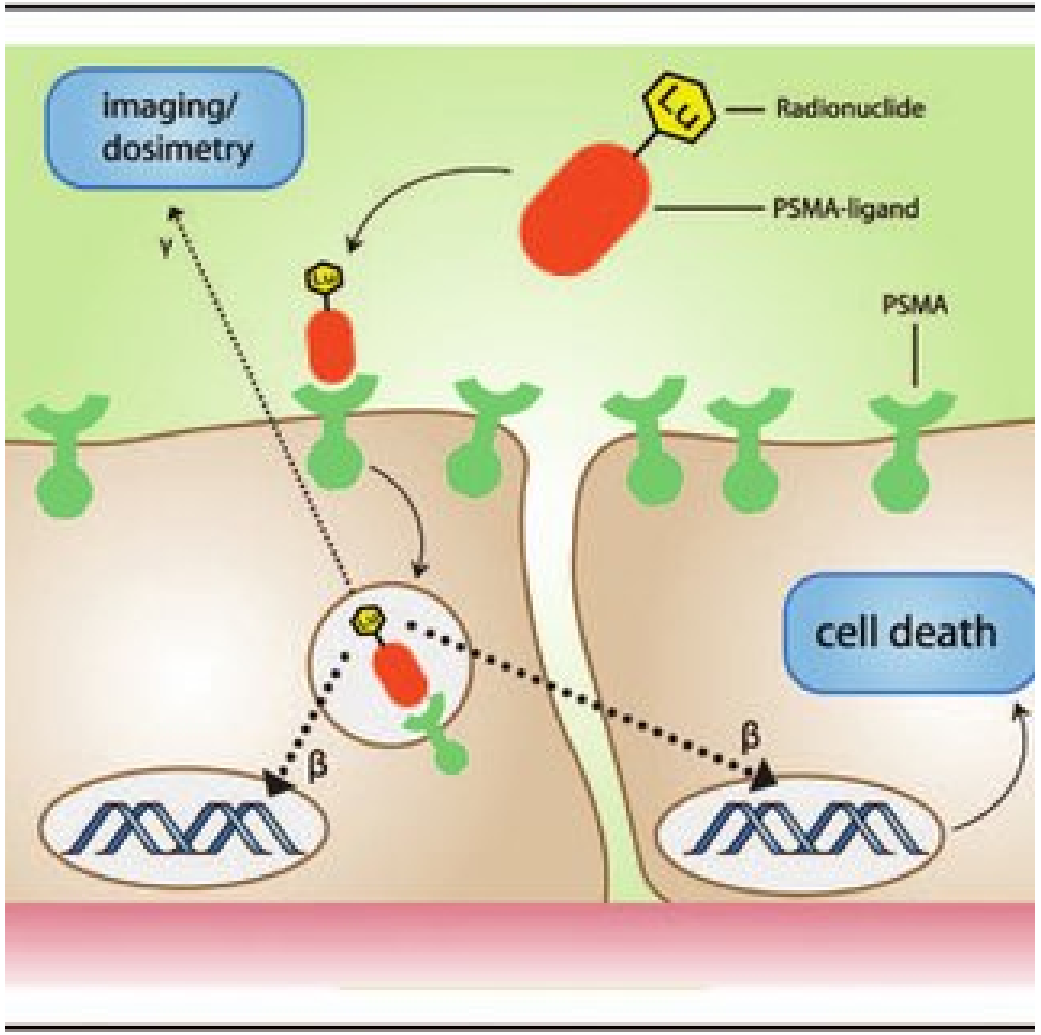
No. at risk																						
Olaparib	162	149	126	116	102	101	82	77	56	53	42	37	26	24	18	11	11	3	2	0	0	0
Physician's choice	83	79	47	44	22	20	13	12	7	6	3	3	3	2	2	1	1	1	1	0	0	0

Future of PARPi

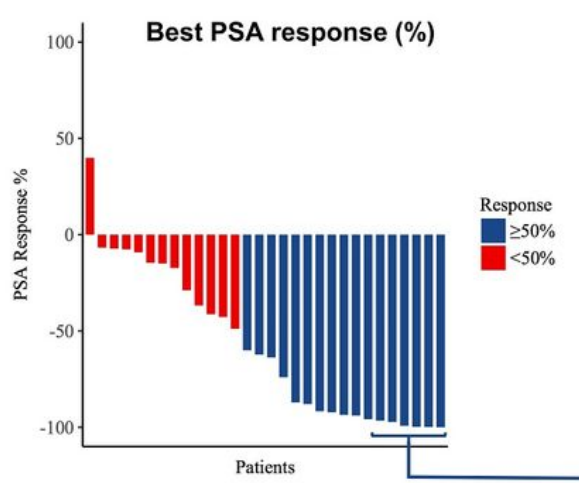
- Combination strategies
  - IO, BAT, AR targeted therapies
- Adjuvant?
- mHSPC
- mHNPC wo ADT

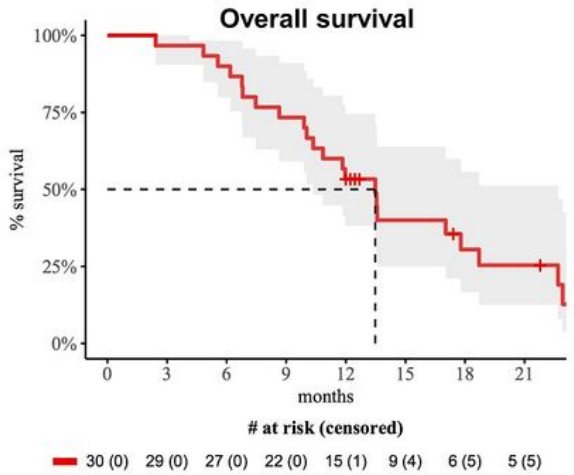
Prostate-Specific Membrane Antigen (PSMA)

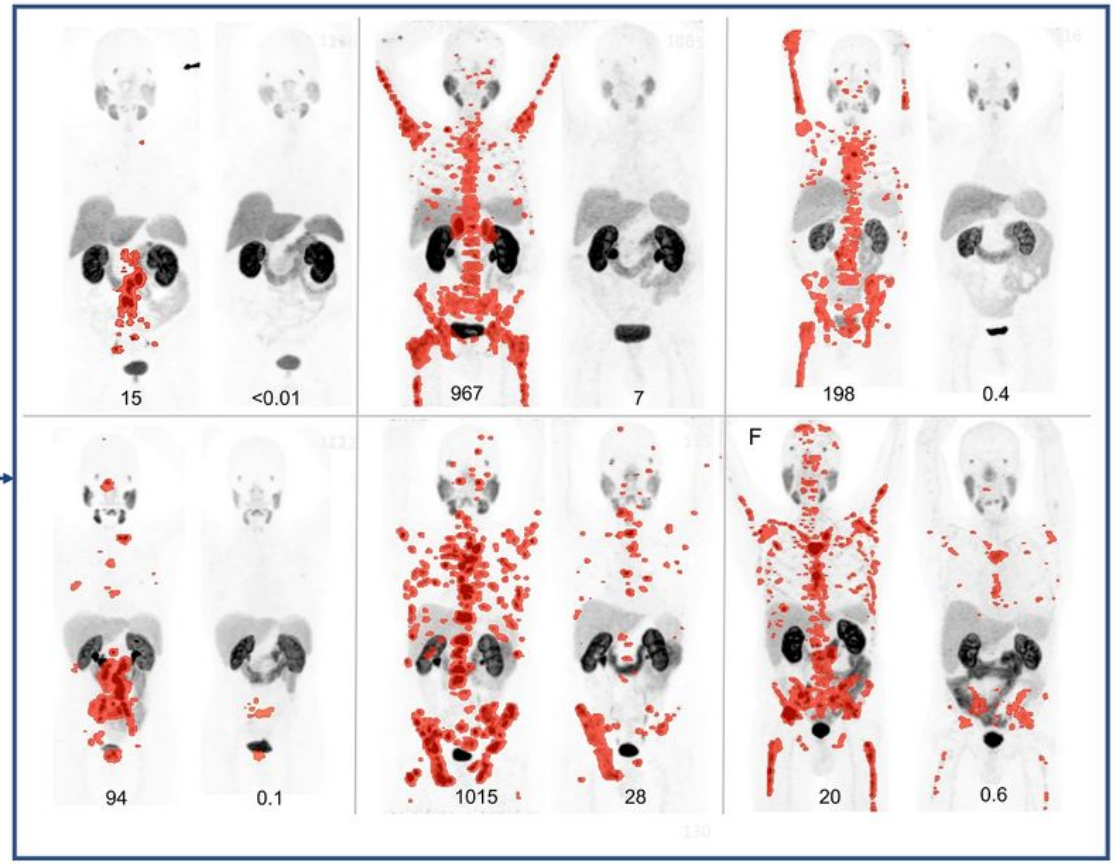
- Transmembrane carboxypeptidase highly expressed on PCa cells.
- Expression has been observed in more than 95% of PCa tumors.
- Direct correlation between expression levels and tumor aggressiveness.



Prostate-specific membrane antigen theranostics: Therapy with lutetium-177 - Scientific Figure on ResearchGate.







^{68}Ga-PSMA11 PET maximum intensity projection (MIP) images at baseline and 3 months after ^{177}Lu-PSMA617 in 6 patients with PSA decline >98%. Any disease with SUVmax over 3 in red.

Michael Hofman et al. J Nucl Med 2018;59:531

PSMA-Based Therapy: ^{177}Lu-PSMA

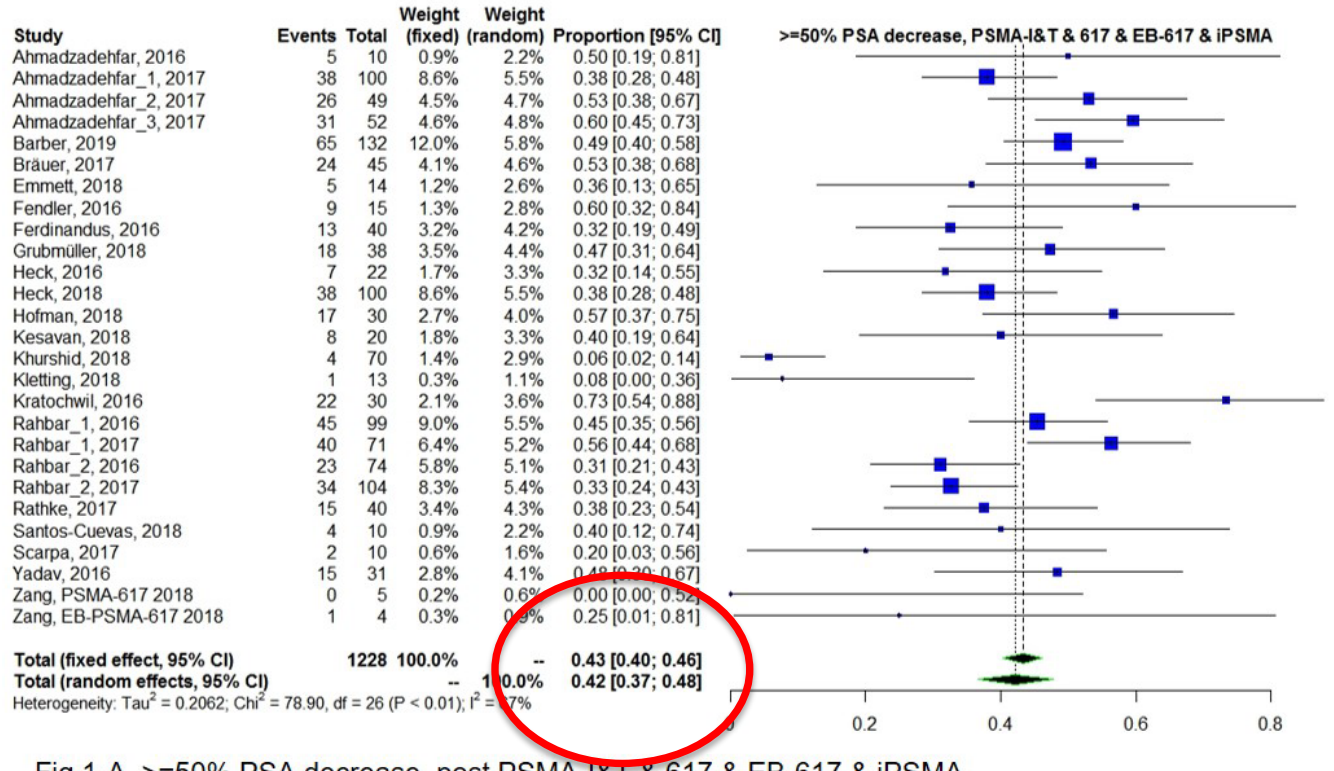


Fig 1-A, >=50% PSA decrease, post PSMA-I&T & 617 & EB-617 & iPSMA

Sadaghiani MS, Sheikhbahaei S, Werner RA, et al. *In Preparation*.

Other Developing Therapies

- CAR-T
- BiTE
- Immune checkpoint combinations
- Wnt inhibition