

# **Neuroendocrine Prostate Cancer Spectrum Diagnosis and Treatment**

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**In lieu of ..**

**Ana Aparicio MD**

**who actually does all this work**

**DAVID H. KOCH CENTER  
FOR APPLIED RESEARCH OF  
GENITOURINARY CANCERS**

THE UNIVERSITY OF TEXAS  
**MD Anderson  
~~Cancer~~ Center**

**Making Cancer History®**

## Disclosures – Eleni Efsthathiou

Research Support/P.I.	Janssen, Sanofi-Genzyme, Astellas/Medivation, Tracon, Oric-Pharma
Scientific Advisory Board Honoraria	Janssen, Sanofi-Genzyme, Tolmar, Takeda, Astra Zeneca, Bayer, Oric Pharma

# Original Clinical Definition of NEPC: a heterogeneous group

Tumors that during the course of androgen deprivation become less dependent on androgen signaling and have invariably a poor prognosis

# Inaccuracies in Terminology

## **Neuroendocrine Prostate Cancer (NEPC):**

Reflective of poor clinical course reminiscent of small cell variant

A confusing term

Neuroendocrine morphology features / markers not required

There are neuroendocrine pathology features not associated with aggressiveness (paneth cell like differentiation)

**“Aggressive variants of prostate cancer”** : less confusing but potentially more contaminated

**“therapy related” neuroendocrine (or small cell) prostate cancer**

Concern : clinicians may withhold potentially effective hormonal therapies

**“Androgen Indifferent Prostate cancer”**: some tumors may still respond to novel androgen signaling inhibition and bias should not be introduced

**“AR Negative Prostate Cancer”**: too limiting

**“Anaplastic prostate cancer”** : term used to denote pleomorphic cytology

Beltran et al CCR 2014

2013 PCF Working group “White Paper”



# Aggressive Variant Prostate Cancer Increased Incidence

Is it indeed? ~ 20%

Greater Awareness

Patients living longer

Development of AVPC as a resistance to novel  
therapies

# NCI Workshop on Lineage Plasticity and Androgen Receptor-Independent Prostate Cancer

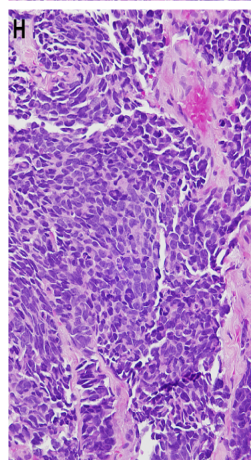
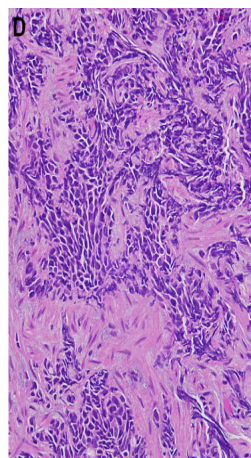
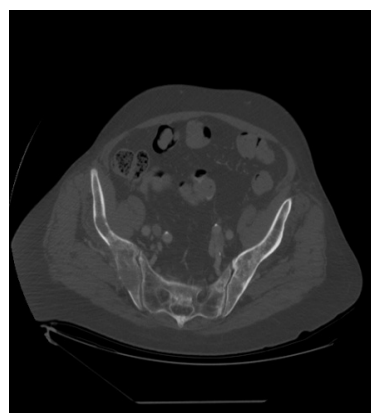
Unmet needs :

- Understanding how lineage plasticity occurs
- Determining the temporal contribution and cooperation of emerging drivers
- Preclinical models that recapitulate biology / recognized phenotypes
- Identification of therapeutic targets and novel trial designs dedicated to the entity as it is defined

# First there was morphology ...

## Small Cell Prostate Carcinoma:

### Aggressive Course and Atypical Clinical Features



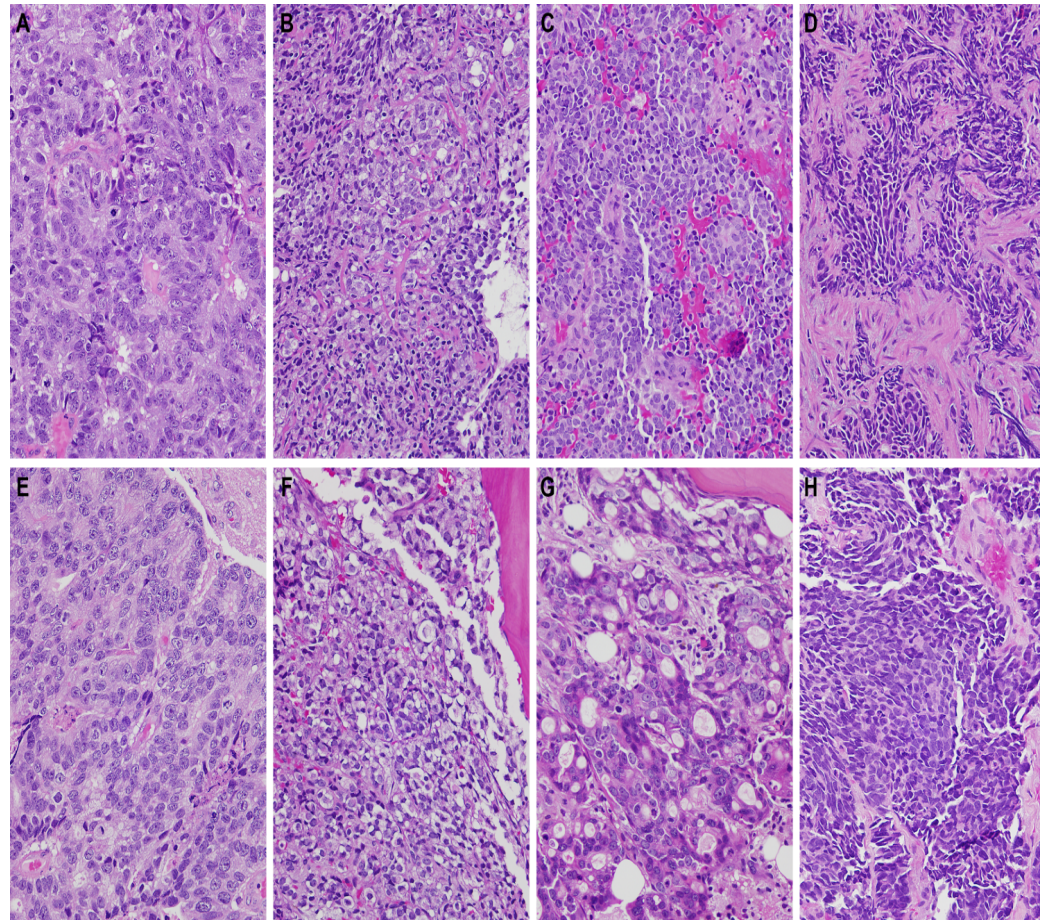
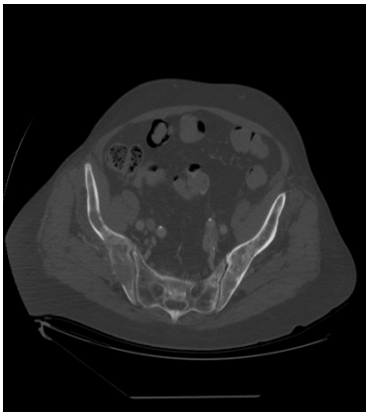
#### Results of a Phase II Study With Doxorubicin, Etoposide, and Cisplatin in Patients With Fully Characterized Small-Cell Carcinoma of the Prostate

By Christos N. Papandreou, Danaï D. Daliani, Peter F. Thall, Shi-Ming Tu, Xuemei Wang, Adriana Reyes, Patricia Troncoso, and Christopher J. Logothetis

*Journal of Clinical Oncology*, Vol 20, No 14 (July 15), 2002: pp 3072-3080

Outcome	Overall	
	No. of Patients/ Total No. of Patients	%
PSA ( $> 4$ ng/mL) (n = 11)	$\geq 80\%$ drop	2/11 18
	$\geq 50-79\%$ drop	2/11 18
	SD	4/11 36
	PD	3/11 27
	Normalization	7/19 37
CEA ( $> 6$ ng/mL) (n = 19)	$\geq 50\%$ drop	8/19 42
	SD	3/19 16
	PD	1/19 5
	Normalization	9/14 64
LDH ( $> 1.5 \times$ UNL) (n = 14)	SD	1/14 7
	PD	4/14 29
	Normalization	6/14 43
Alkaline phosphatase ( $>$ UNL) (n = 14)	SD	3/14 21
	PD	5/14 36
	Normalization	6/14 43
Measurable disease (n = 36)	PR	22/36 61
	SD	3/36 8
	PD	11/36 31
Bone metastases (n = 22)	Improvement	6/22 27
	SD	10/22 46
	PD	6/22 27

**Then comes clinical presentation .**  
**Aggressive Variant Prostate Cancer:**  
**Clinical course association with SCPC**



## ***Aggressive Variant Prostate Cancer Clinicopathological Criteria (AVPC-C)***

1. Small cell prostate carcinoma
2. Visceral metastases only
3. Lytic bone metastases
4. Bulky nodes or prostate mass
5. Low PSA relative to volume
6. NE markers & serum CEA or LDH
7. Primary castration-resistance

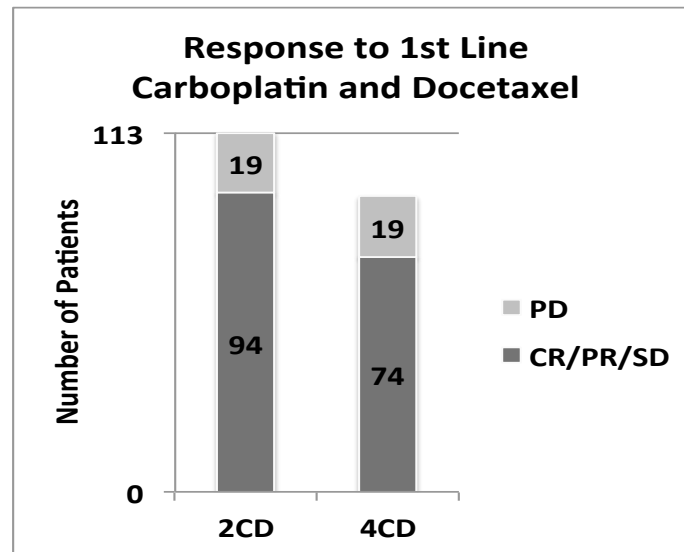


# Aggressive Variant Prostate Cancer

Hypothesis:

Do shared *clinical features* of small cell prostate carcinoma predict for shared platinum based chemotherapy combination *sensitivity*?

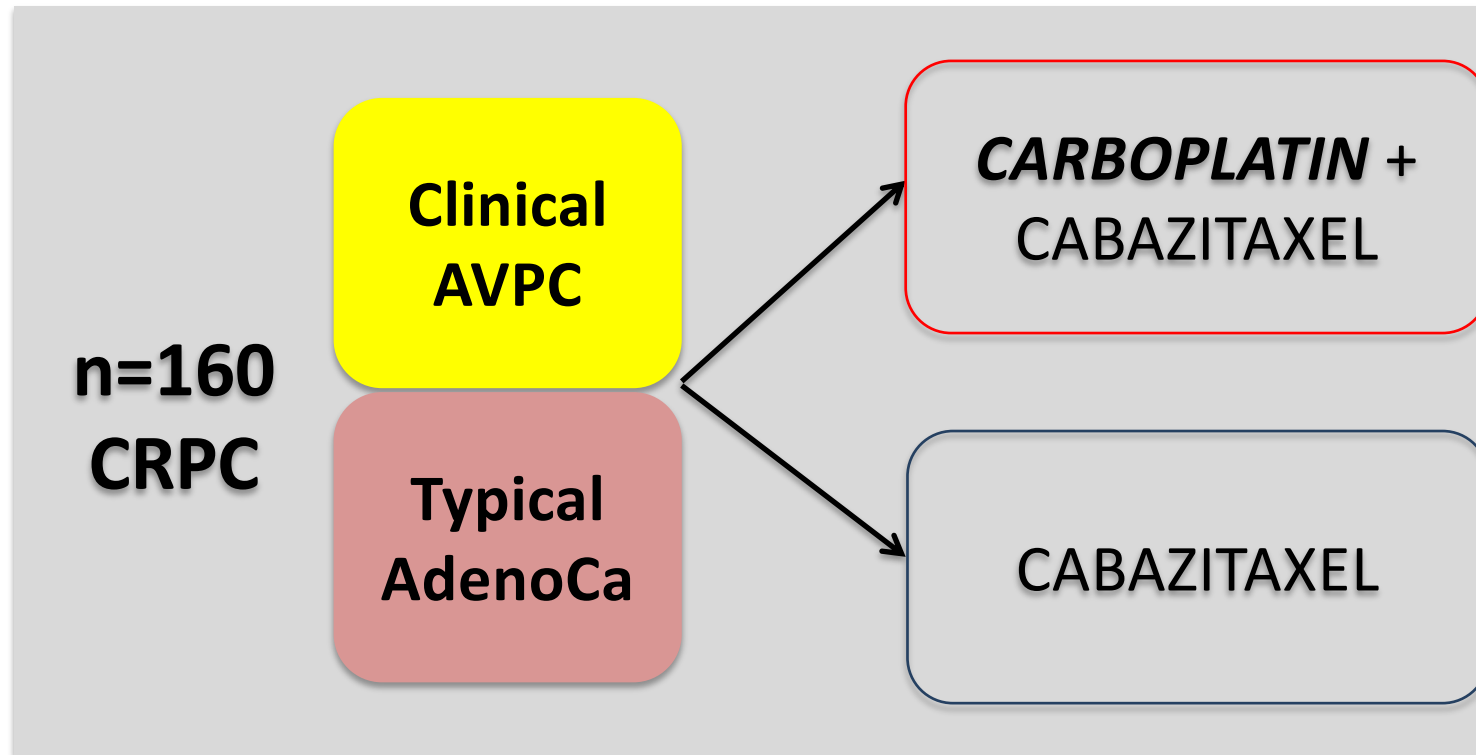
# The Clinically Defined AVPC Share the Chemotherapy Sensitivity of the SCPC



## Conclusion

*The clinically defined Aggressive Variant Prostate Cancers share the **benefit from platinum based chemotherapy** of the small cell prostate carcinomas*

# Cabazitaxel +/- Carboplatin in mCRPC

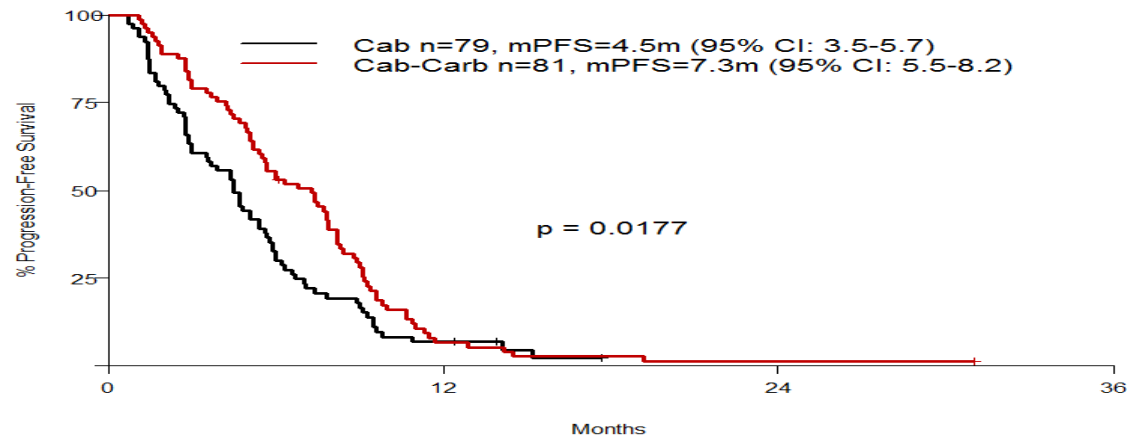


**MDACC/Karmanos**

PI: Paul Corn, MD, PhD



# Carboplatin added to Cabazitaxel improves the mPFS of men with mCRPC

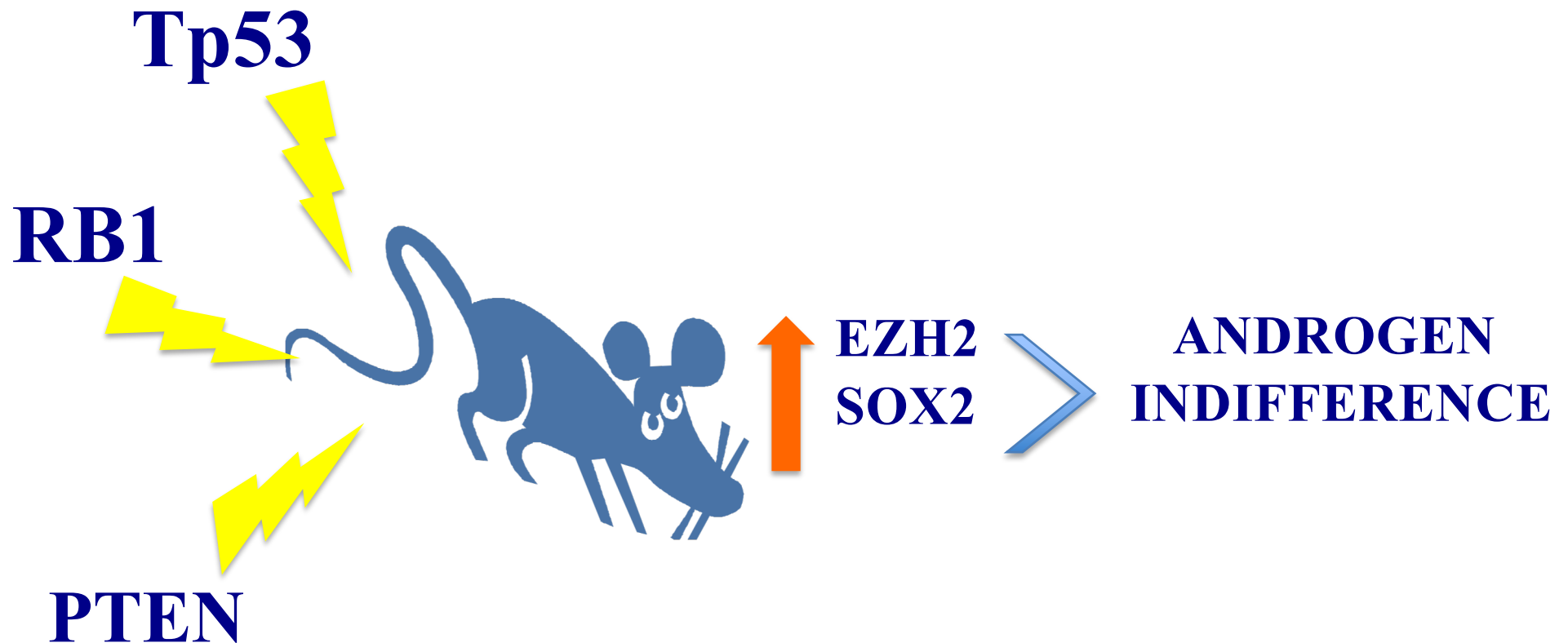


Factor	Level	N	HR (95% CI)	P value
All patients		160	0.68 (0.49, 0.94)	0.018
ECOG	0	43	0.36 (0.19, 0.7)	0.003
	1 or 2	117	0.8 (0.55, 1.17)	0.245
Rsp to Prior DTX	No	23	0.47 (0.18, 1.19)	0.111
	Yes	23	0.95 (0.38, 2.39)	0.906
AVPC C ITT	0	74	0.74 (0.46, 1.21)	0.228
	1	86	0.58 (0.37, 0.89)	0.013

HR (CC vs. C)

*Aparicio et al in press*

# Preclinical Models Support Significance of a Combined Tumor Suppressor Defect Signature



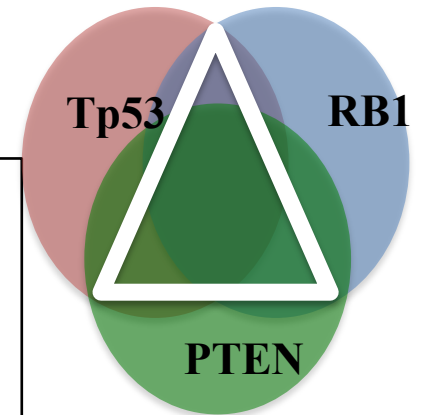
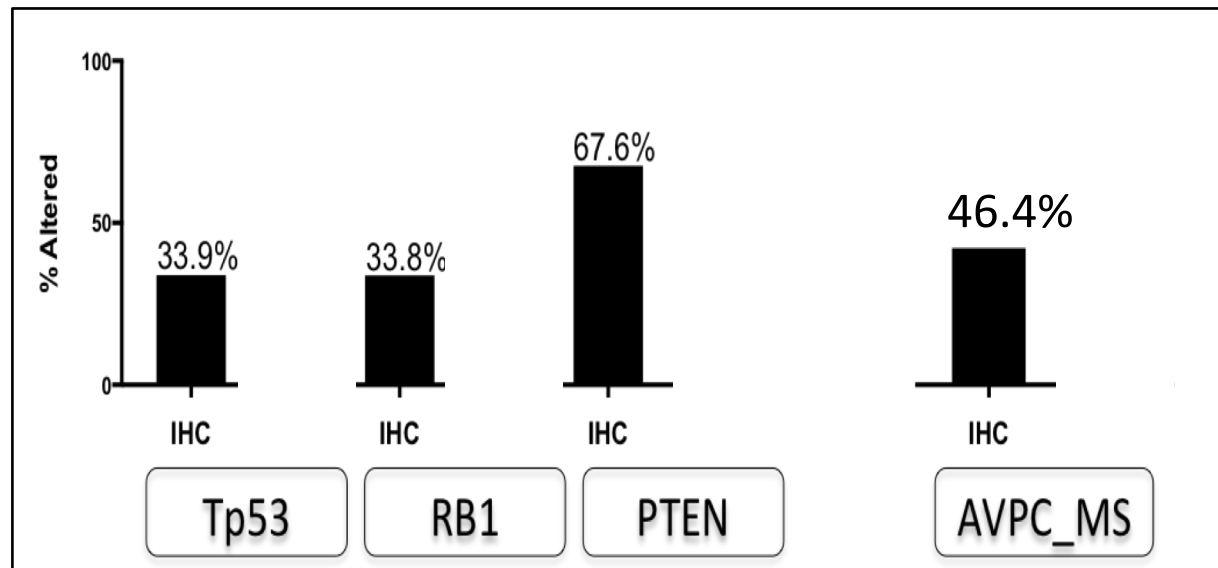
Yu Ku, *Science* 2017; Mu, *Science* 2017

# Exploring AVPC Molecular Signature in Solid Tumor Biopsies: Immunohistochemistry

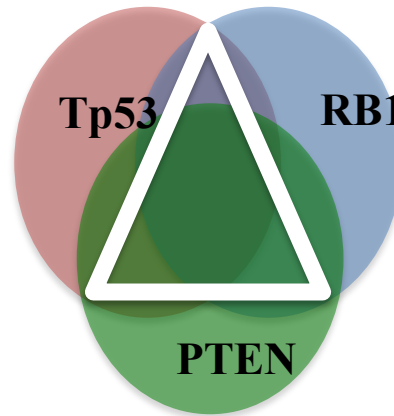
Patient Accession #  
Tissue Sample Name

Tumor Biopsies

N= 64 patients IHC

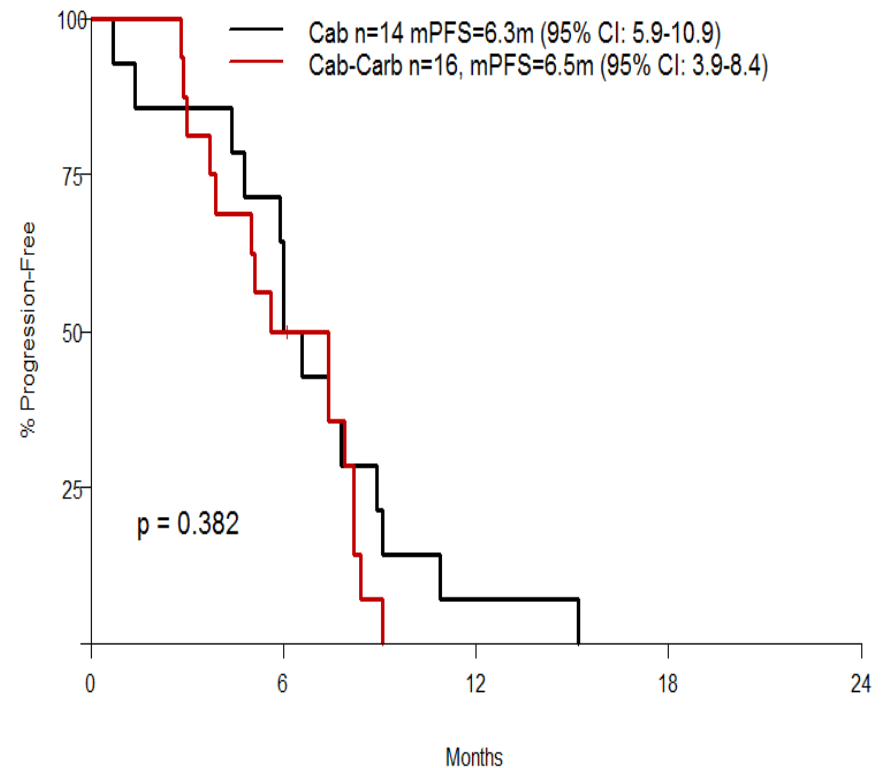
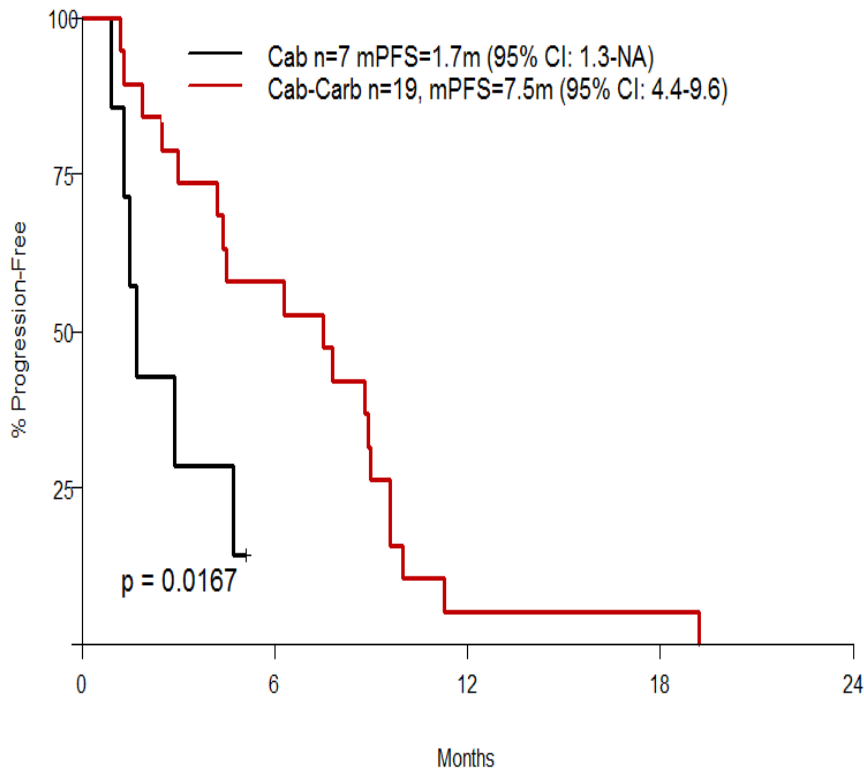


# The AVPC-MS\_IHC Predicts for Benefit from the Addition of Carboplatin

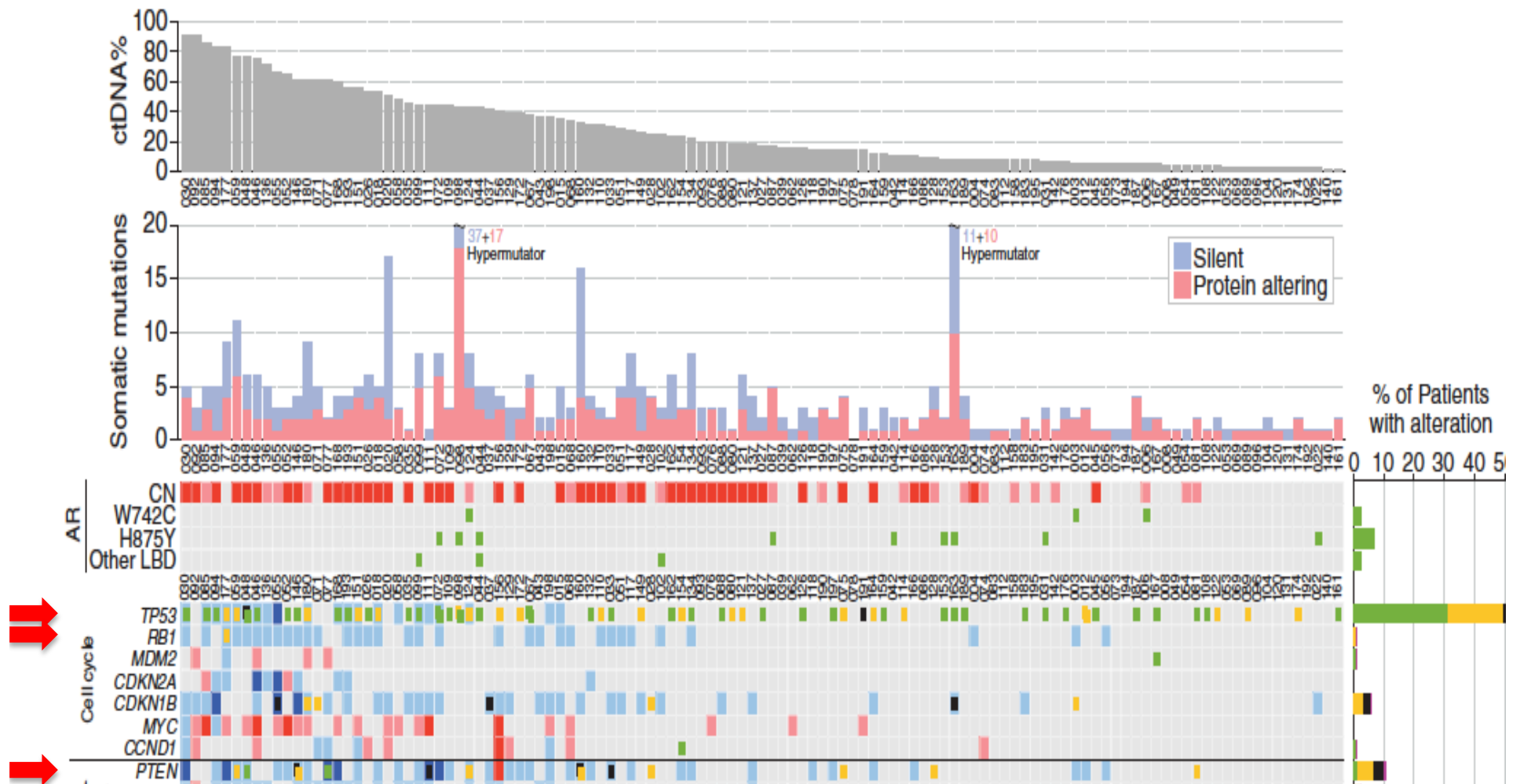


**AVPC\_MS\_IHC  
POSITIVE**

**AVPC\_MS\_IHC  
NEGATIVE**

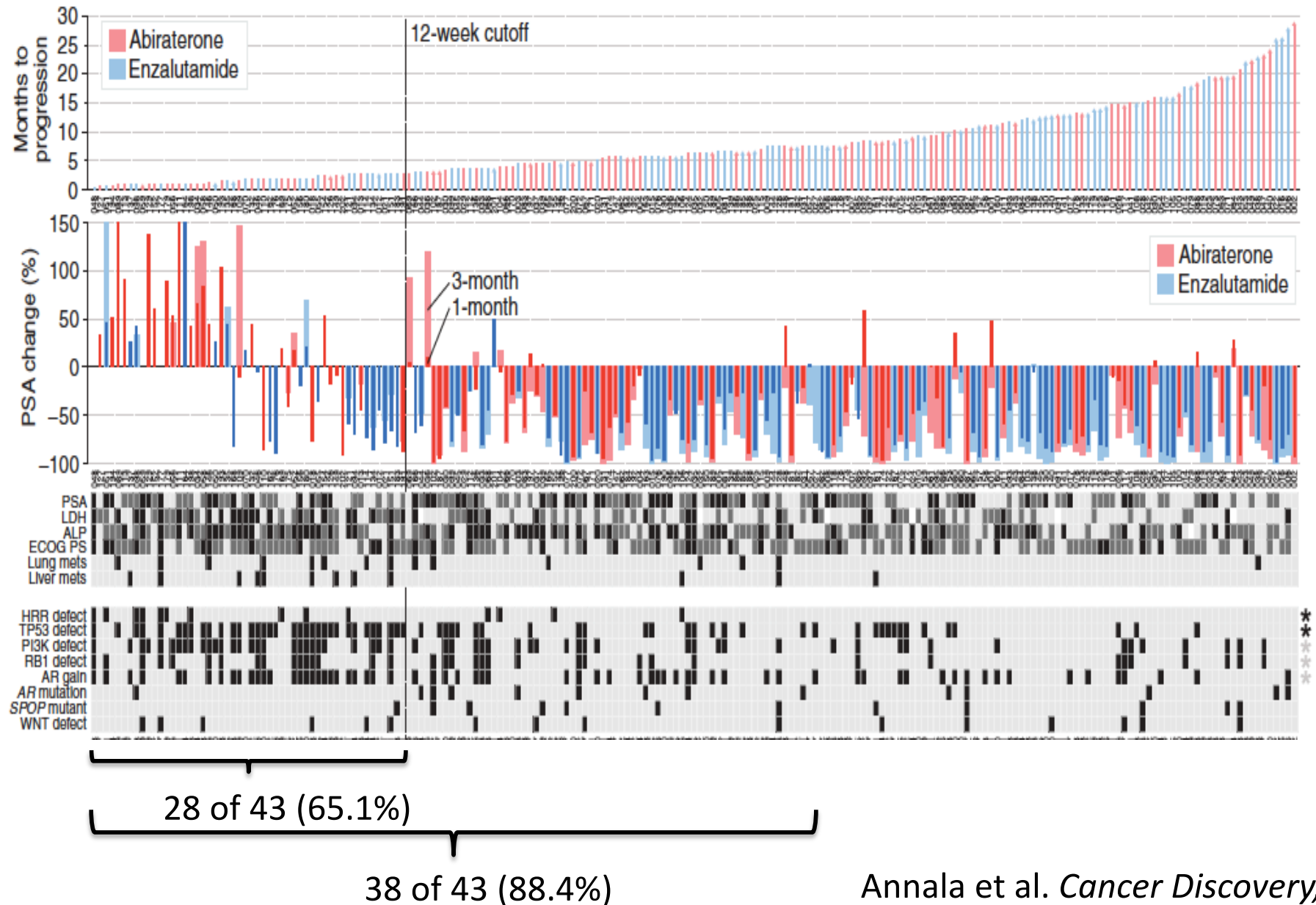


# AVPC-MS in ctDNA of Men with mCRPC in Abiraterone vs Enzalutamide Clinical Trial

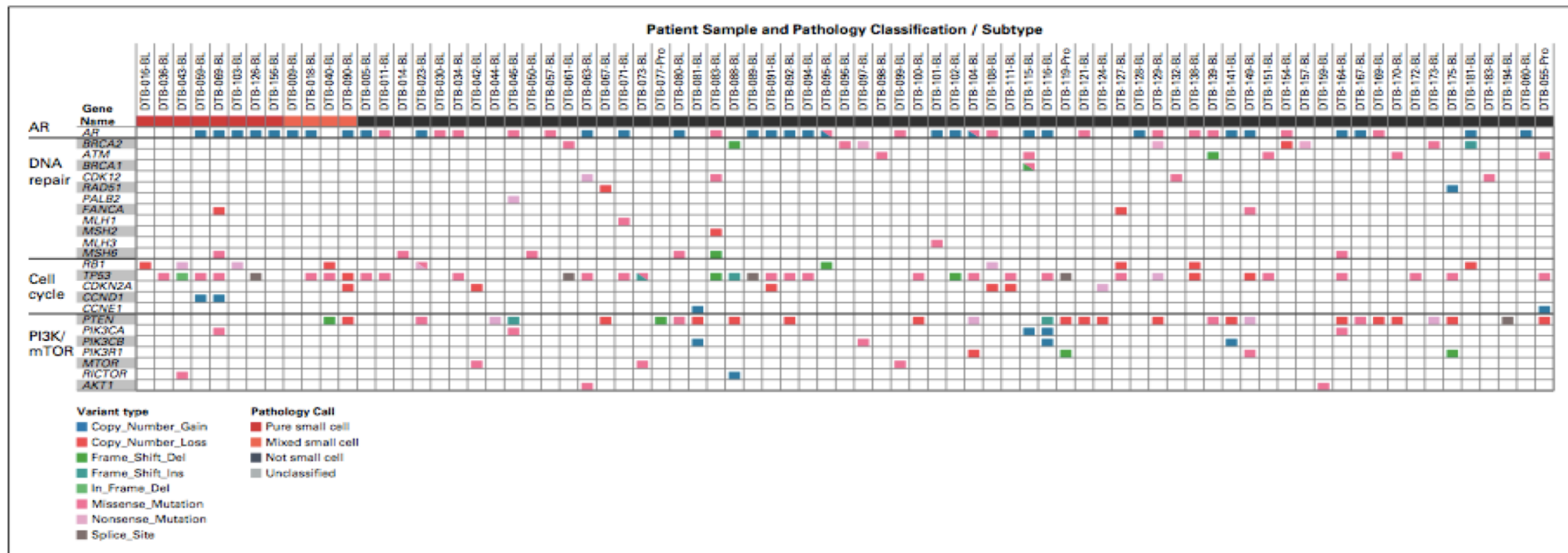


**43 (37.4%) of 115 had AVPC\_MS in ct DNA**

# AVPC-MS\_ctDNA is Associated with Androgen Indifference



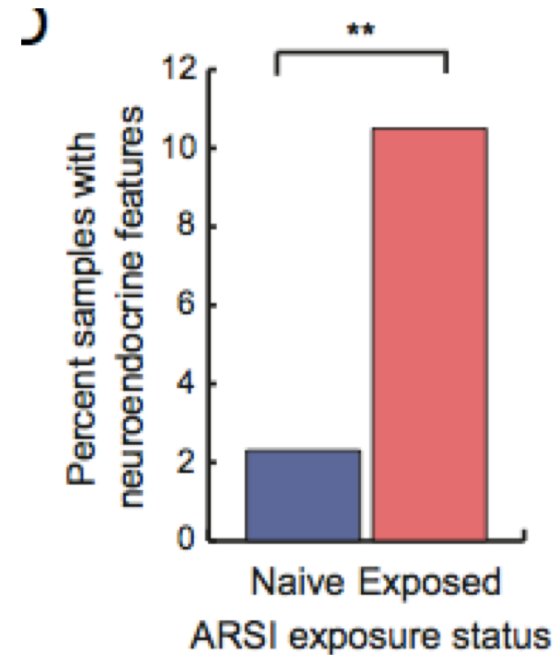
# Clinical and Genomic Characterization of t-SCNC differentiation



Genomic alterations in the DNA repair pathway were nearly mutually exclusive with t-SCNC differentiation ( $P = .035$ )

# Association of common genomic alteration with overall survival and time on treatment with first-line ARSI

Gene/pathway alteration	Univariate <i>P</i> value for survival from first-line ARSI (CPE, <i>n</i> = 128 or as indicated)	for time on treatment with first-line ARSI (CPE, <i>n</i> = 108 or as indicated)
RB1	<b>0.002 (CPE 0.768)</b>	<b>&lt;0.001 (CPE 0.818)</b>
TP53	0.072 (CPE 0.605)	<b>0.046 (CPE 0.609)</b>
WNT pathway	0.115	0.153
ETS fusion	0.159	0.206
APC	0.255	0.167
CTNNB1	0.274	0.448
ATM	0.331	0.850
BRCA2	0.327	0.418
BRCA2/BRCA1/ATM	0.495	0.611
AKT1	0.558	0.053
RNF43	0.614	0.844
AR	0.658	<b>0.005 (CPE 0.651)</b>
PTEN	0.676	0.412
PI3K pathway	0.699	0.138
PIK3CA	0.716	0.165
PIK3R1	0.752	0.892
PIK3CB	0.799	0.277
BRCA1	0.809	0.998
NEPC score	0.218 ( <i>n</i> = 99)	0.930 ( <i>n</i> = 80)
AR signaling score	0.847 ( <i>n</i> = 99)	0.847 ( <i>n</i> = 80)
RB1 loss score	<b>&lt;0.001 (<i>n</i> = 99)</b>	<b>0.014 (<i>n</i> = 80)</b>
CCP score	<b>0.002 (<i>n</i> = 99)</b>	<b>0.045 (<i>n</i> = 80)</b>
AR-V7 SRPM	0.524 ( <i>n</i> = 75)	0.329 ( <i>n</i> = 56)





# Current State from a practical perspective

## **Diagnosis**

Clinical criteria help identify the aggressive variant

(caveat: contamination by other molecular subtypes)

Morphology : several guidelines now recommend sampling metastases

Molecular subtyping requires validation and is not ready for prime time

# Current State

Treatment of a clinical AVPC

Consideration of platinum based combinatorial chemotherapy is valid

(evidence remains weak)

Point for non- purists: contamination with DDR driven tumors is not a practical concern if platinum is offered)

# APCCC 2017 – Identification of AVPC

**Table 9 – Which of the following criteria would you use to define poor prognosis, aggressive variant metastatic castration-resistant prostate cancer (mCRPC) putting aside pure small cell prostate cancer?**

Which of the following criteria would you use to define poor prognosis, aggressive variant mCRPC putting aside pure small cell prostate cancer:	Yes (%)	Only in combination with other unfavourable factors (%)	No (%)	I do not believe poor prognosis, aggressive variant mCRPC is a clinically meaningful entity (%)	Abstain (%)
Neuro-endocrine differentiation on a tumour biopsy and/or low or absent androgen receptor expression	71	27	0	2	0
Exclusive visceral metastases	70	20	6	4	0
Rapid progression without correlation with PSA kinetics	63	31	4	2	0
Low PSA levels relative to tumour burden	45	47	6	2	0
Predominantly lytic bone metastases	45	39	14	2	0
Short response to androgen deprivation therapy ( $\leq 12$ mo) for metastatic prostate cancer	34	60	4	2	0
Bulky tumour masses	21	65	12	2	0

# APCCC 2017 – Treatment of AVPC

First-line treatment of AVPC (putting aside pure small cell carcinoma) based on clinical criteria:

58% standard mCRPC treatment

42% platinum-based chemotherapy

# Our Expectations for 4<sup>th</sup> APCCC meeting as clinicians

- Precise molecular characterization to help identify subtypes to move away from “lumping together”
- This will enable therapy development
- Can transformation be predicted early on and thus potentially averted ? *(hint:look within non-psa progressors in nmCRPC studies)*
- How should these patients be followed

# Remembering a Philanthropist

“To indulge our benevolent affections constitutes the perfection of human nature”

Adam Smith



David H Koch : May 3, 1940 –August 23 2019

“I d like my epitaph to say that David Koch did his best to make the world a better place and that he hopes his wealth will help people long after he has passed away”