

# Treatment choice: castration resistant state

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# 2000 landscape

**LOCAL  
TREATS**

**BIOCHEMICAL  
RELAPSE**

**METASTASES**

**ADT**

**AntiAndrogens**

**Mitoxantrone**

**HSPC**

**CRPC**



# 2016 landscape

**LOCAL TREATS**

**BIOCHEMICAL RELAPSE**

**METASTASES**

**ADT**

**AntiAndrogens**

**HSPC**

**CRPC**

**Docetaxel**

**Abiraterone**

**Enzalutamide**

**Docetaxel**

**Cabazitaxel**

**Enzalutamide**

**Abiraterone**

**Ra 223**



# 2016 landscape

LOCAL TREATS

BIOCHEMICAL RELAPSE

METASTASES

**Cabazitaxel vs Docetaxel in Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer: A Three-Arm Phase III Study (FIRSTANA)**

Oliver Sartor,<sup>1</sup> Stéphane Oudard,<sup>2</sup> Lisa Sengelev,<sup>3</sup> Gedde Daugaard,<sup>4</sup> Fred Saad,<sup>5</sup> Steinbjørn Hansen,<sup>6</sup> Marie Hjelm-Eriksson,<sup>7</sup> Jacak Jassem,<sup>8</sup> Antoine Thierry-Vuillemin,<sup>9</sup> Crazie Caffo,<sup>10</sup> Daniel Castellano,<sup>11</sup> Paul N. Mainwaring,<sup>12</sup> John Bernard,<sup>13</sup> Liji Shen,<sup>14</sup> Mustapha Chadja,<sup>15</sup> Karim Fizazi<sup>16</sup>

<sup>1</sup>Tulane Cancer Center, New Orleans, LA, USA; <sup>2</sup>George Pompidou European Hospital, René Descartes University, Paris, France; <sup>3</sup>Heller Hospital, Lyngby, Denmark; <sup>4</sup>Copenhagen University Hospital, Copenhagen, Denmark; <sup>5</sup>Medical University Health Center, Montreal, Canada; <sup>6</sup>Copenhagen University Hospital, Copenhagen, Denmark; <sup>7</sup>Karolinska University Hospital, Stockholm, Sweden; <sup>8</sup>Medical University of Gdansk, Gdansk, Poland; <sup>9</sup>ICHI Major Biocenter, Boulogne, France; <sup>10</sup>Medical Oncology Department, Santa Clara Hospital, North, Italy; <sup>11</sup>University Hospital 12 de Octubre, Madrid, Spain; <sup>12</sup>North Cancer Care, Brisbane, Queensland, Australia; <sup>13</sup>Royal Free Hospital, London, UK; <sup>14</sup>Harvard University, Boston, MA, USA; <sup>15</sup>Harvard University, Boston, MA, USA; <sup>16</sup>Royal Free Hospital, London, UK; <sup>17</sup>Guilford Rousey, University of Paris Sud, Villejuif, France

ASCO ANNUAL MEETING '16

CRPC

Abiraterone

Enzalutamide

Cabazitaxel

Cabazitaxel

Enzalutamide

Abiraterone

Ra 223

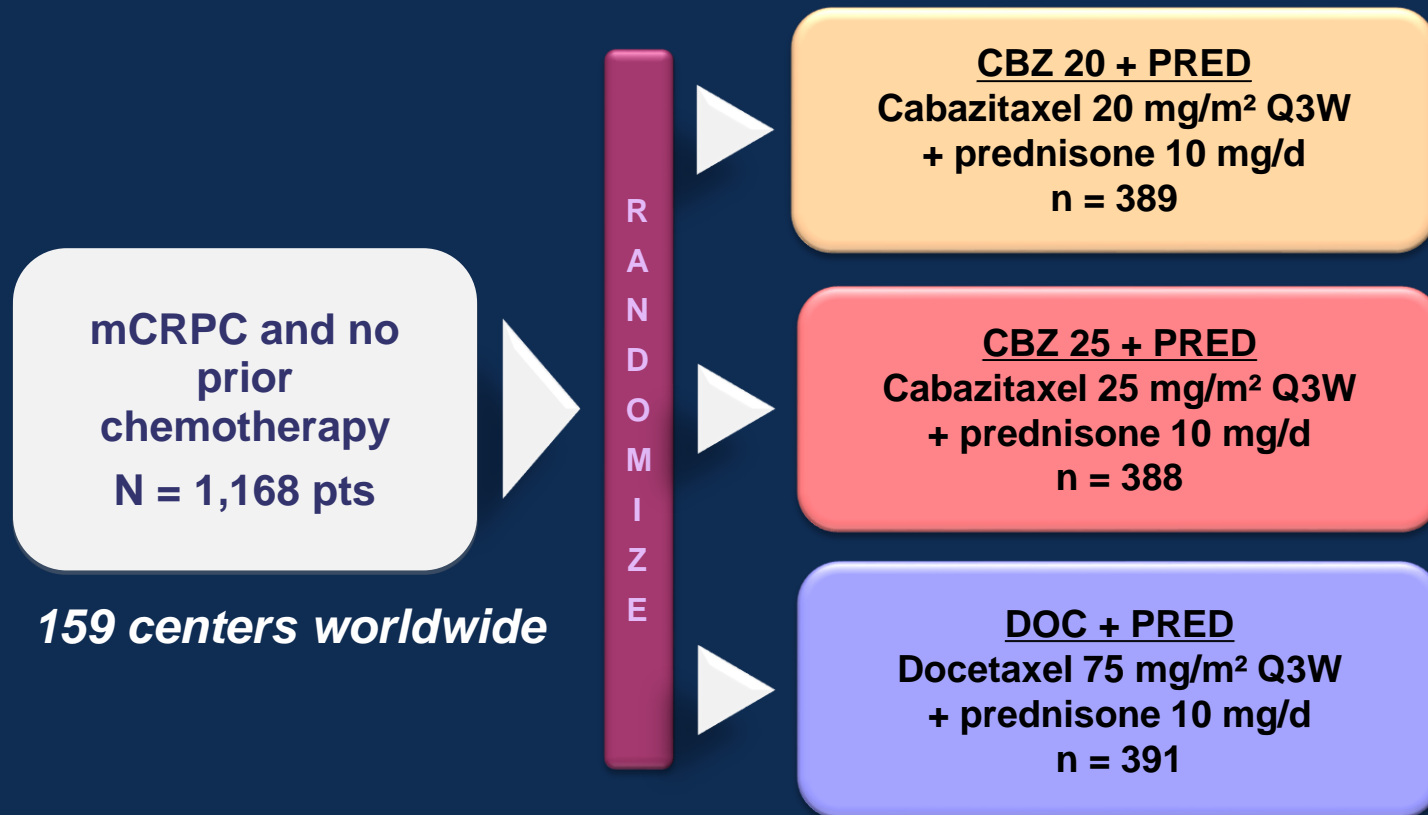


# Cabazitaxel vs Docetaxel in Chemotherapy-Naïve Patients with Metastatic Castration-Resistant Prostate Cancer: A Three-Arm Phase III Study (FIRSTANA)

**Oliver Sartor,<sup>1</sup> Stephane Oudard,<sup>2</sup> Lisa Sengeløv,<sup>3</sup> Gedske Daugaard,<sup>4</sup> Fred Saad,<sup>5</sup> Steinbjørn Hansen,<sup>6</sup> Marie Hjelm-Eriksson,<sup>7</sup> Jacek Jassem,<sup>8</sup> Antoine Thiery-Vuillemin,<sup>9</sup> Orazio Caffo,<sup>10</sup> Daniel Castellano,<sup>11</sup> Paul N. Mainwaring,<sup>12</sup> John Bernard,<sup>13</sup> Liji Shen,<sup>14</sup> Mustapha Chadjaa,<sup>15</sup> Karim Fizazi<sup>16</sup>**

<sup>1</sup>Tulane Cancer Center, New Orleans, LA, USA; <sup>2</sup>George Pompidou European Hospital, Rene Descartes University, Paris, France; <sup>3</sup>Herlev Hospital, Herlev, Denmark; <sup>4</sup>Copenhagen University Hospital, Copenhagen, Denmark; <sup>5</sup>Montreal University Health Centre, Montreal, Canada; <sup>6</sup>Odense University Hospital, Odense, Denmark; <sup>7</sup>Karolinska University Hospital, Stockholm, Sweden; <sup>8</sup>Medical University of Gdansk, Gdansk, Poland; <sup>9</sup>CHU Minjoz Besançon, Besançon, France; <sup>10</sup>Medical Oncology Department, Santa Chiara Hospital, Trento, Italy; <sup>11</sup>University Hospital 12 de Octubre, Madrid, Spain; <sup>12</sup>Icon Cancer Care, Brisbane, Queensland, Australia; <sup>13</sup>Sanofi Genzyme, Cambridge, MA, USA; <sup>14</sup>Sanofi Genzyme, Bridgewater, NJ, USA; <sup>15</sup>Sanofi Genzyme, Paris, France; <sup>16</sup>Institut Gustave Roussy, University of Paris Sud, Villejuif, France

# FIRSTANA: Study Design



# FIRSTANA: Endpoints & Statistical Plan

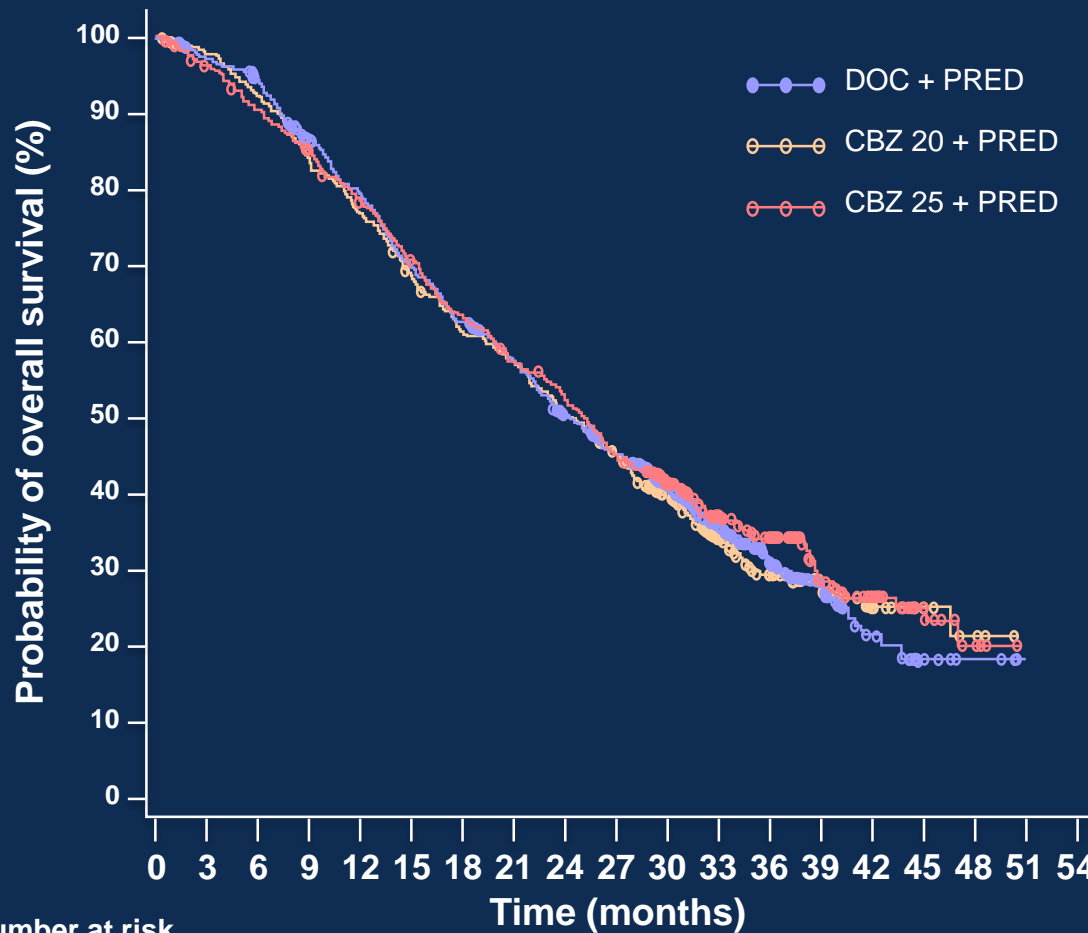
## Endpoints

- **Primary:** Overall Survival
- **Secondary:** Safety, PFS (based on tumor, PSA, or pain progression or death), tumor response, PSA response, pain response, time to skeletal-related events, HRQoL, pharmacokinetics/pharmacogenomics
- **Exploratory:** cfDNA

## Statistical plan

- OS superiority of CBZ over DOC (HR: 0.75)
- 774 deaths needed to achieve 90% power
- Interim analyses at 1/3 and 2/3 of 774 deaths

# FIRSTANA: Overall Survival



Median OS, months (95% CI)

**DOC + PRED** 24.3 (22.18–27.60)

**CBZ 20 + PRED** 24.5 (21.75–27.20)

**CBZ 25 + PRED** 25.2 (22.90–26.97)

**CBZ 20 vs DOC**

HR 1.009 (0.85–1.197)

P = 0.9967

**CBZ 25 vs DOC**

HR 0.97 (0.819–1.16)

P = 0.7574

Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
DOC + PRED	39	36	33	30	24	19	13	7	5	3	3	3	3	3	3	3	3	3	3
CBZ 20 + PRED	38	35	31	29	23	19	13	7	5	3	3	3	3	3	3	3	3	3	3
CBZ 25 + PRED	39	36	33	30	24	19	13	7	5	3	3	3	3	3	3	3	3	3	3



# FIRSTANA: Laboratory Abnormalities

Patients, n/N <sup>a</sup> (%)	<b>DOC + PRED</b> N = 387	<b>CBZ 20 + PRED</b> N = 369	<b>CBZ 25 + PRED</b> N = 391
<b>Neutropenia</b>			
All Grades	341/383 (89.0)	240/368 (65.2)	335/391 (85.7)
Grade 3–4	302/383 (78.9)	139/368 (37.8)	276/391 (70.6)
<b>Anemia</b>			
All Grades	382/384 (99.5)	366/368 (99.5)	390/391 (99.7)
Grade 3–4	21/384 (5.5)	24/368 (6.5)	34/391 (8.7)
<b>Thrombocytopenia</b>			
All Grades	125/384 (32.6)	130/368 (35.3)	177/390 (45.4)
Grade 3–4	6/384 (1.6)	6/368 (1.6)	12/390 (3.1)

<sup>a</sup> Patients with post-baseline value for the parameter

# 2016 landscape

**LOCAL TREATS**

**BIOCHEMICAL RELAPSE**

**METASTASES**

**ADT**

**AntiAndrogens**

**HSPC**

**CRPC**

**Docetaxel**

**Abiraterone**

**Enzalutamide**

**Docetaxel**

**Cabazitaxel**

**Enzalutamide**

**Abiraterone**

**Ra 223**



drug	comparator	OS $\Delta$	HR	p
docetaxel	MITOX	2.5 mos	0.76	<0.001
abiraterone	PLACEBO+PDN	4.4 mos	0.81	0.003
enzalutamide	PLACEBO	4.0 mos	0.77	0.0002
radium-223	PLACEBO	4.6 mos	0.74	0.03



# Choice key points



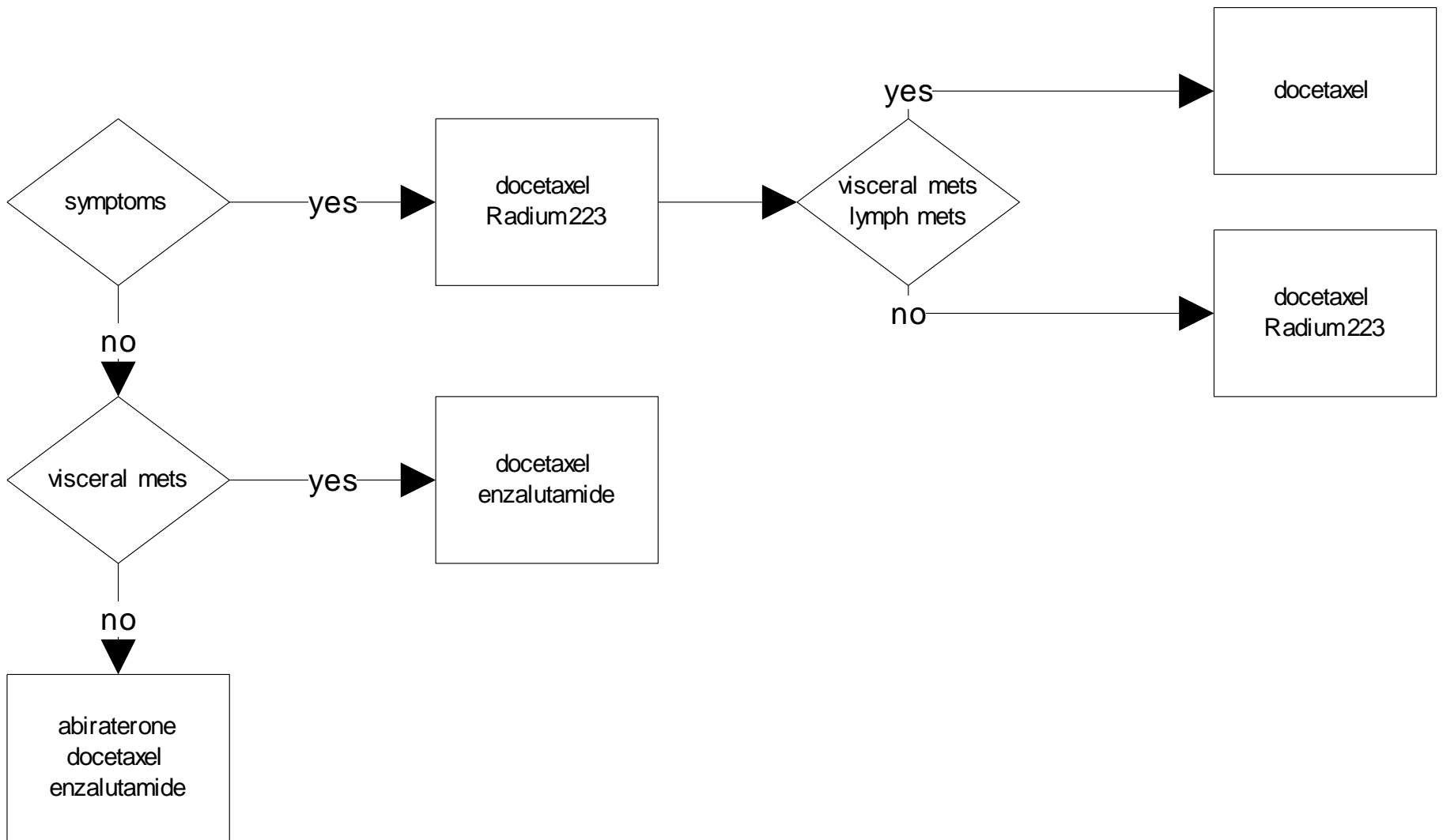
- Disease oriented
- Patient oriented



# mCRPC front line

	PS2	ELDERLY	VISCERAL METS	SYMPTOMATIC
TAX327	√	√	√	√
COU-302	√	√		
PREVAIL	√	√	√	
ALSYMPCA	√	√		√





# mCRPC front line

	PS2	ELDERLY	VISCERAL METS	SYMPTOMATIC
TAX327	√	√	√	√
COU-302	√	√		
PREVAIL	√	√	√	
ALSYMPCA	√	√		√

## Choice criteria

- Disease oriented
  - Visceral mets
- Patient oriented
  - Symptoms
  - Comorbidities (cardiovascular, diabetes, seizure)
- Patients preferences and feelings
- Clinicians preferences and feelings



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**Docetaxel**

**Cabazitaxel**

**Enzalutamide**

**Abiraterone**

**Ra 223**





drug	comparator	OS $\Delta$	HR	p
cabazitaxel	MITOX	2.4 mos	0.70	<0.001
abiraterone	PLACEBO+PDN	3.9 mos	0.65	<0.001
enzalutamide	PLACEBO	4.8 mos	0.63	<0.001
Radium 223	PLACEBO	3.1 mos	0.71	0.003



# mCRPC second line

	PS2	ELDERLY	VISCERAL METS	SYMPTOMATIC
TROPIC	√	√	√	√
COU-301	√	√	√	√
AFFIRM	√	√	√	√
ALSYMPCA	√	√		√

Choice criteria?

**FIRST LINE TREATMENT**



## 1ST LINE

## 2 ND LINE

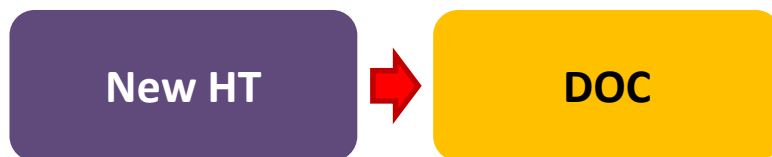
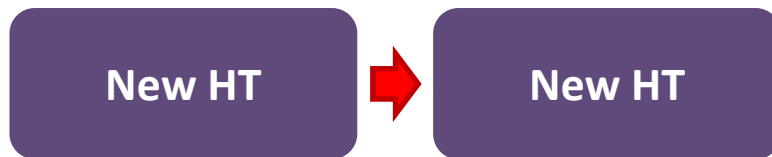
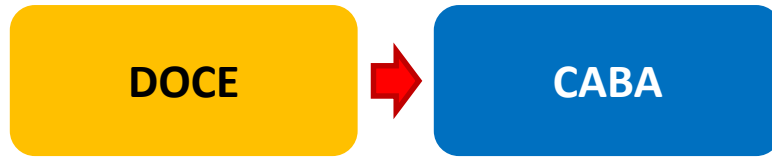
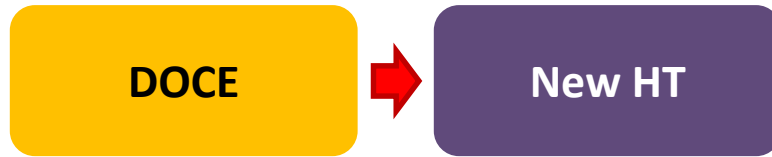


- To date no clear evidence supports the superiority of one drug over another
- The only decision-making issues should be patient-oriented
  - Burden of 1st-line-related toxicity
  - Time of recovery
  - 2nd-line toxicity profile (vs comorbidities)
  - Patient's preference
- 2nd-line toxicity profile (vs comorbidities)
- Patient's preference



## 1ST LINE

## 2 ND LINE



- To date no clear evidence supports the superiority of one drug over another
- The only decision-making issues should be patient-oriented
  - Burden of 1st-line-related toxicity
  - Time of recovery
  - 2nd-line toxicity profile (vs comorbidities)
  - Patient's preference



<div style="text-align: right;">Second line</div> <div style="text-align: left;">First line</div>	DOCETAXEL (TAX327)	CABAZITAXEL (TROPIC)	ABIRATERONE (COU-302)	ENZALUTAMIDE (AFFIRM)
DOCETAXEL		✓	✓	✓
ABIRATERONE	?	?		?
ENZALUTAMIDE	?	?	?	



Original article

Sequencing new agents after docetaxel in patients with metastatic castration-resistant prostate cancer

Francesca Maines<sup>a</sup>, Orazio Caffo<sup>a,\*</sup>, Antonello Veccia<sup>a</sup>, Chiara Trentin<sup>a</sup>, Giampaolo Tortora<sup>b</sup>, Enzo Galligioni<sup>a</sup>, Emilio Brià<sup>b</sup><sup>a</sup> Medical Oncology, S. Chiara Hospital, Largo Medaglie d'oro 1, 38122 Trento, Italy<sup>b</sup> Medical Oncology, Azienda Ospedaliera Universitaria Integrata, University of Verona, Piazzale LA. Scuro 10, 37134 Verona, Italy25 Potential Studies identified

1 Study excluded because of exclusion criteria (chemo-naïve setting)

11 Studies excluded because of monthly OS rates were not available

13 Studies included in the analysis (1022 pts)

HNA → HNA  
(481 pts)HNA → CABA  
(312 pts)CABA → HNA  
(229 pts)

7 Studies (329 pts) evaluating the sequence ABI → ENZ

3 Studies (80 pts) evaluating the sequence ENZ → ABI

5 Studies (296 pts) evaluating the sequence ABI → CABA

1 Study (16 pts) evaluating the sequence ENZ → CABA

3 Studies (208 pts) evaluating the sequence CABA → ABI

1 Study (21 pts) evaluating the sequence CABA → ENZ

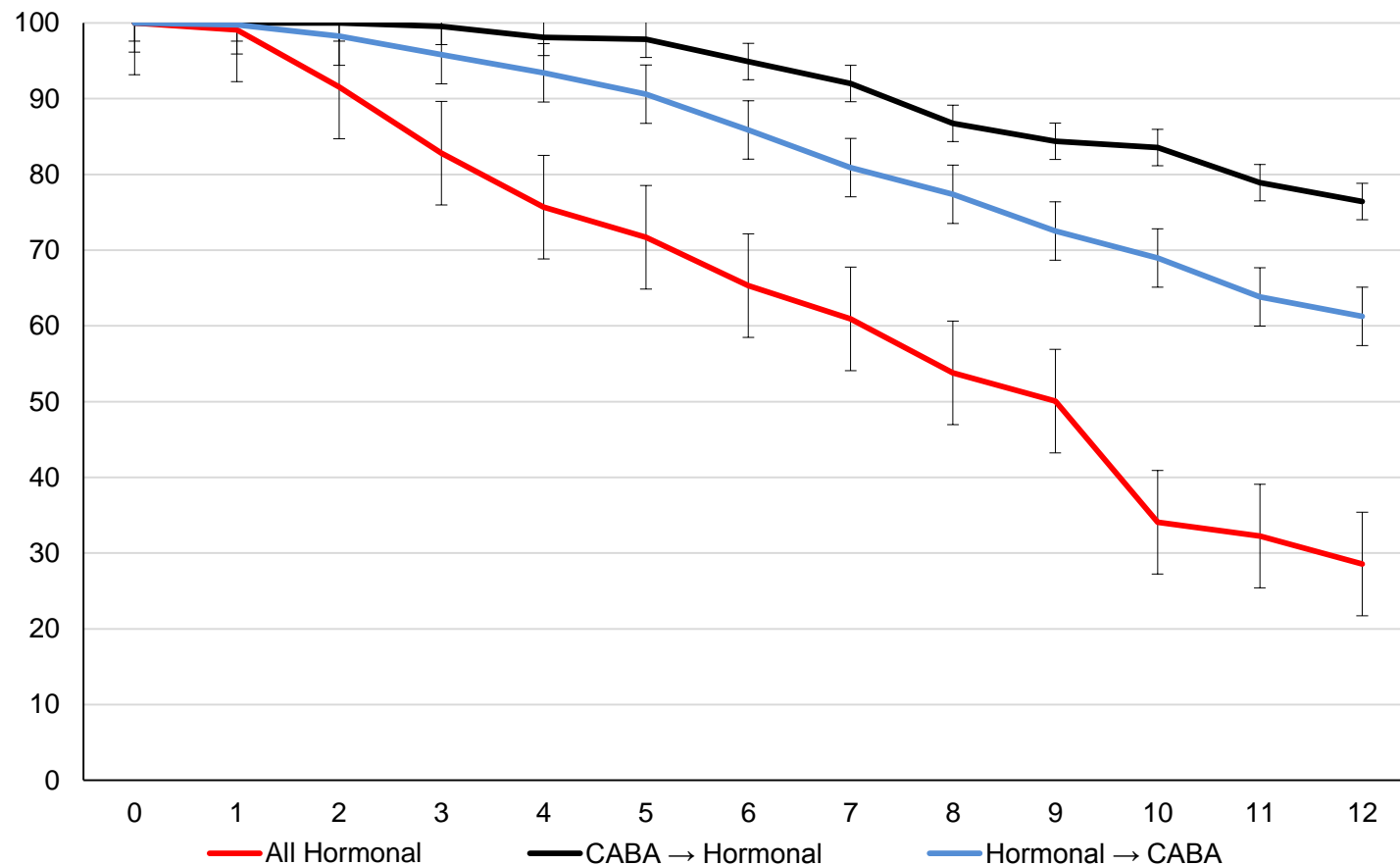


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# OS by 3 sequencing strategies





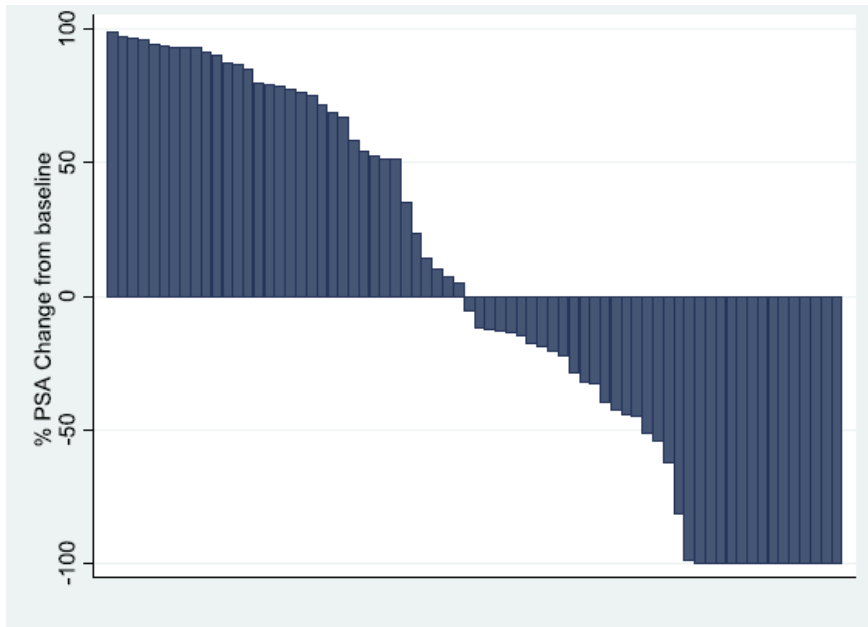
Available at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

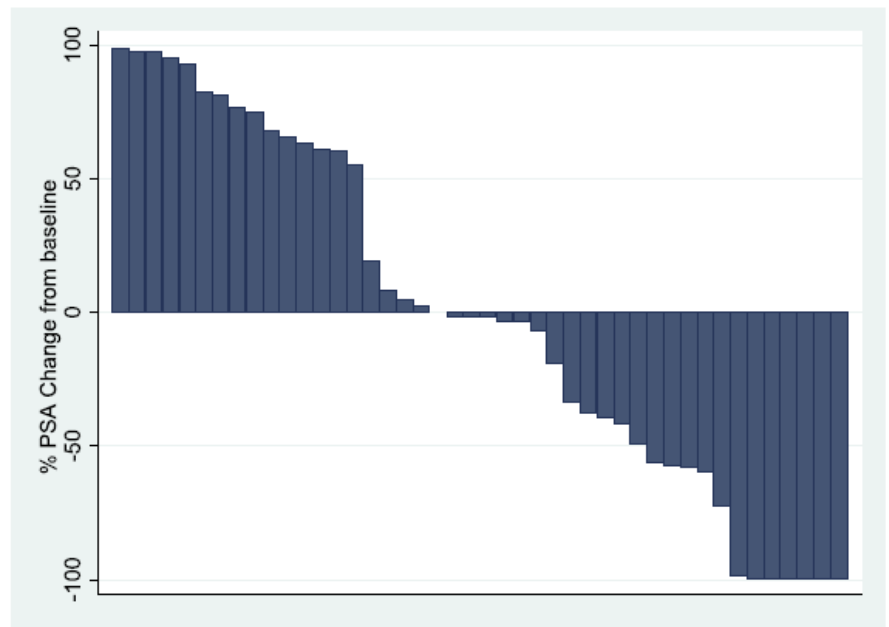
journal homepage: [www.ejcancer.com](http://www.ejcancer.com)



## The influence of prior novel androgen receptor targeted therapy on the efficacy of cabazitaxel in men with metastatic castration-resistant prostate cancer



NO ART



ART







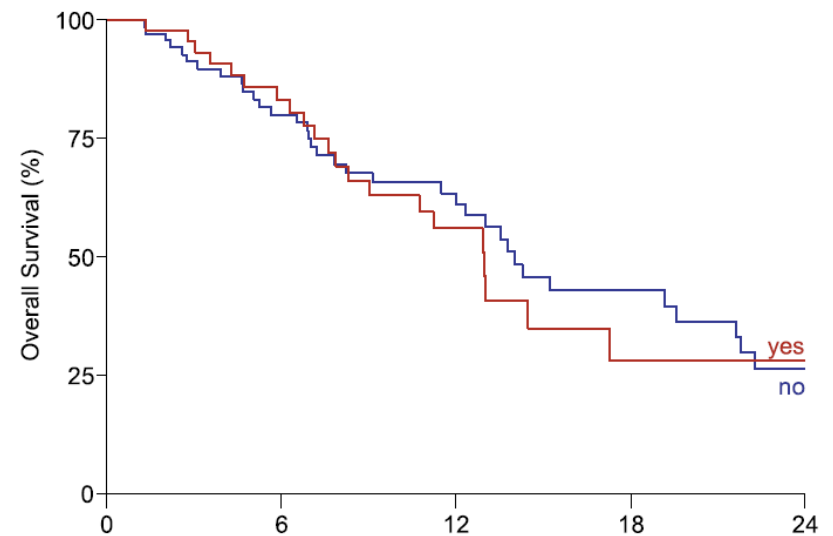
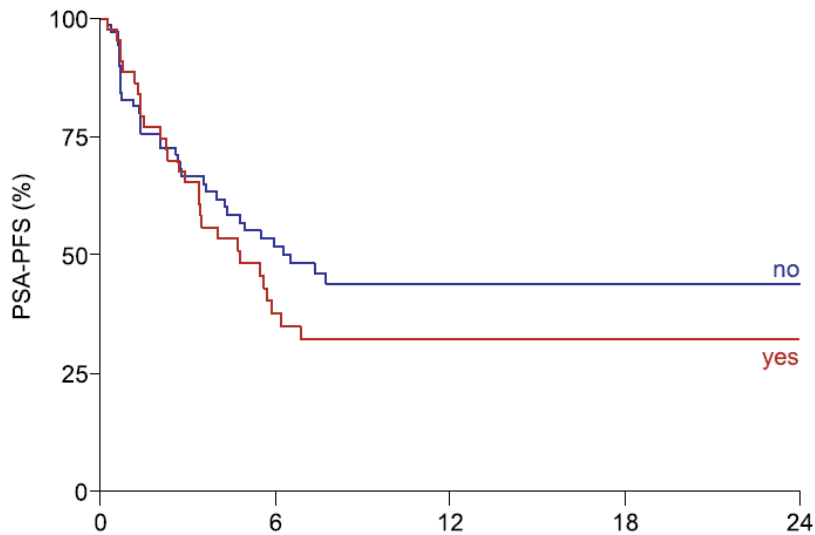
Available at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.ejcancer.com](http://www.ejcancer.com)



## The influence of prior novel androgen receptor targeted therapy on the efficacy of cabazitaxel in men with metastatic castration-resistant prostate cancer



# BIOLOGICAL EVIDENCES



# 2016 landscape

LOCAL TREATS

BIOCHEMICAL RELAPSE

METASTASES

AD

AntiAnd

HS

## AR-V7 As a Clinical Biomarker in CRPC

Emmanuel S. Antonarakis, M.D.

*Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

ABSTRACT # 5050 | ASCO ANNUAL MEETING '16

CRPC

Docetaxel

Abiraterone

Enzalutamide

Docetaxel

Cabazitaxel

Enzalutamide

Abiraterone

Ra 223



# AR-V7 As a Clinical Biomarker in CRPC

Emmanuel S. Antonarakis, M.D.

*Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD*

PRESENTED AT: **ASCO ANNUAL MEETING '16**

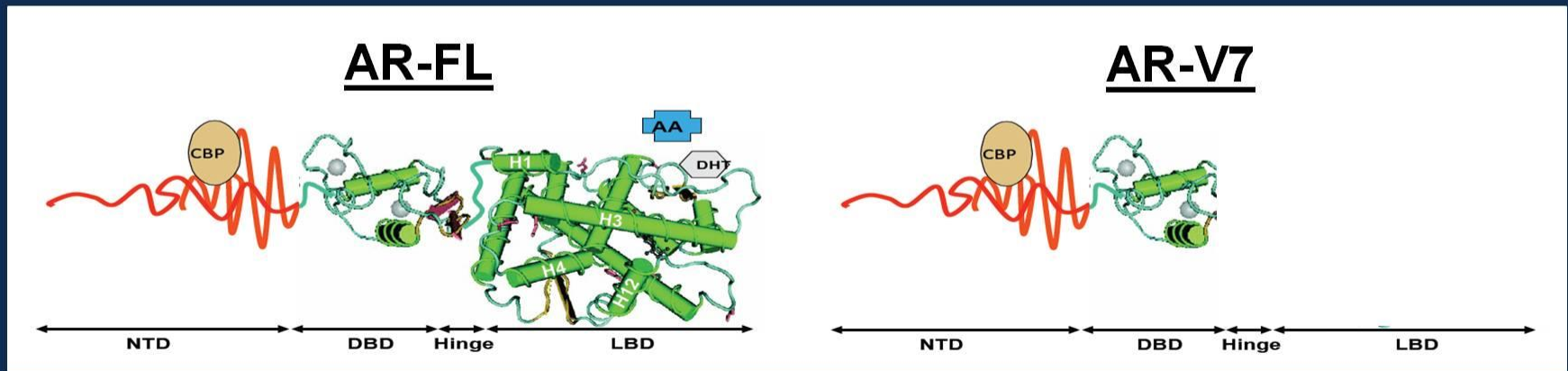
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Presented By Emmanuel Antonarakis at 2016 ASCO Annual Meeting



# AR-V7 in mCRPC

Androgen receptor variant 7 (AR-V7) is a truncated form of the AR that lacks the LBD, the target of abiraterone and enzalutamide, but remains constitutively active as a transcription factor



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Presented by: **Emmanuel S. Antonarakis, M.D.**



ORIGINAL ARTICLE

# AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

N Engl J Med 2014;371:1028-38.

Original Investigation

## Androgen Receptor Splice Variant 7 and Efficacy of Taxane Chemotherapy in Patients With Metastatic Castration-Resistant Prostate Cancer

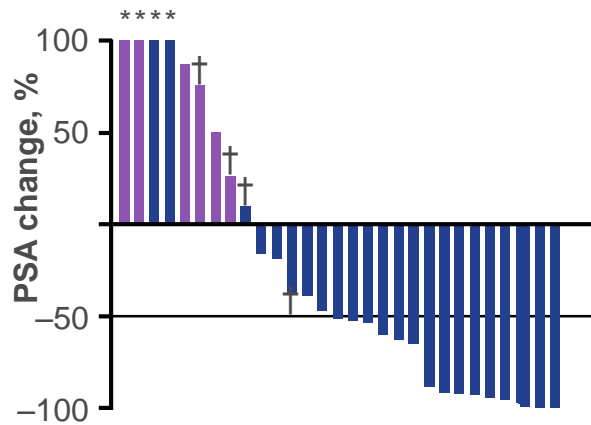
*JAMA Oncol.* doi:10.1001/jamaoncol.2015.1341

Published online June 4, 2015.



# PSA response

## Abiraterone



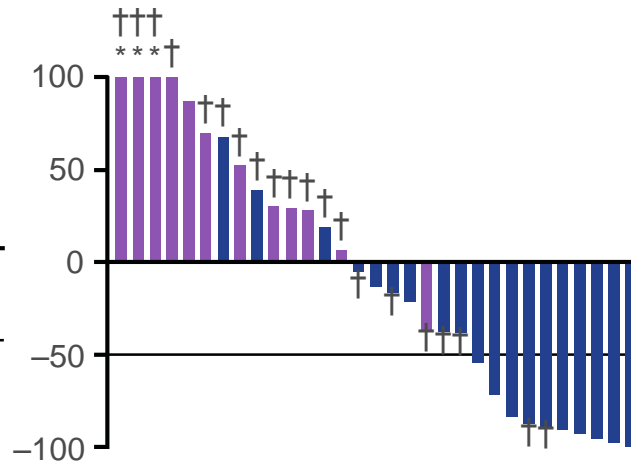
### PSA response rate

**AR-V7 positive: 0%** (95% CI: 0-46%)

**AR-V7 negative: 68.0%** (95% CI: 46-85%)

$P=0.004$

## Enzalutamide



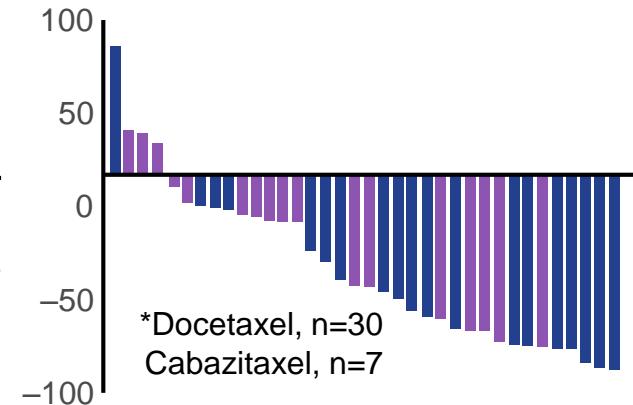
### PSA response rate:

**AR-V7 positive: 0%** (95% CI: 0-26%)

**AR-V7 negative: 52.6%** (95% CI: 29-76%)

$P=0.004$

## Taxane\*



### PSA response rate:

**AR-V7 positive: 41%** (95% CI: 18-67%)

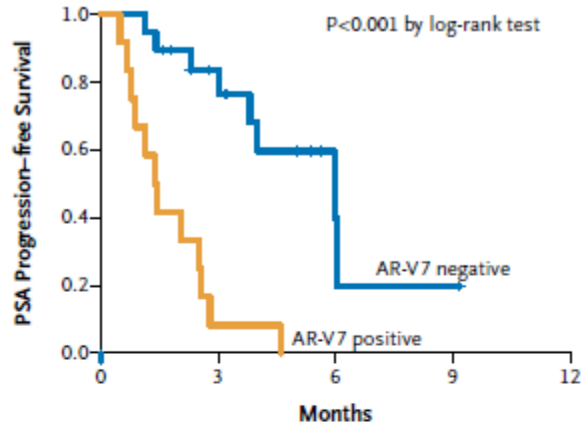
**AR-V7 negative: 65%** (95% CI: 41-85%)

$P=0.19$

■ AR-V7 positive ■ AR-V7 negative



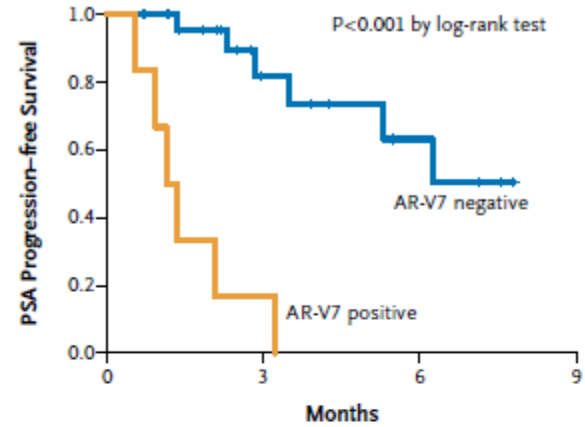
**A Enzalutamide-Treated Patients**



**No. at Risk**

AR-V7 negative	19	12	2	1	0
AR-V7 positive	12	1	0	0	0

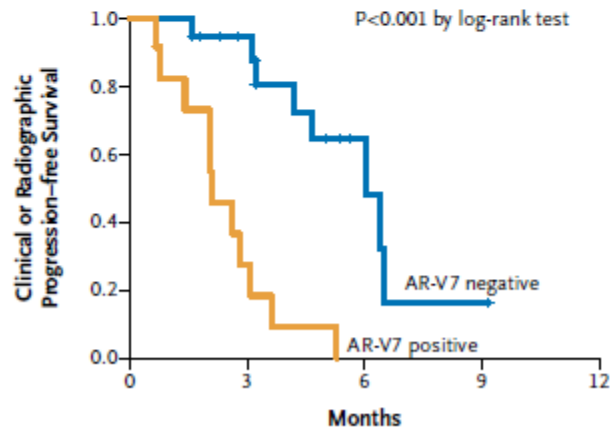
**B Abiraterone-Treated Patients**



**No. at Risk**

AR-V7 negative	25	10	5	0
AR-V7 positive	6	1	0	0

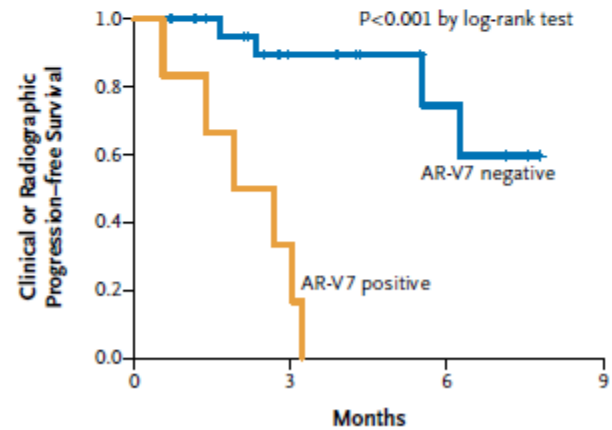
**C Enzalutamide-Treated Patients**



**No. at Risk**

AR-V7 negative	19	14	4	1	0
AR-V7 positive	12	3	0	0	0

**D Abiraterone-Treated Patients**



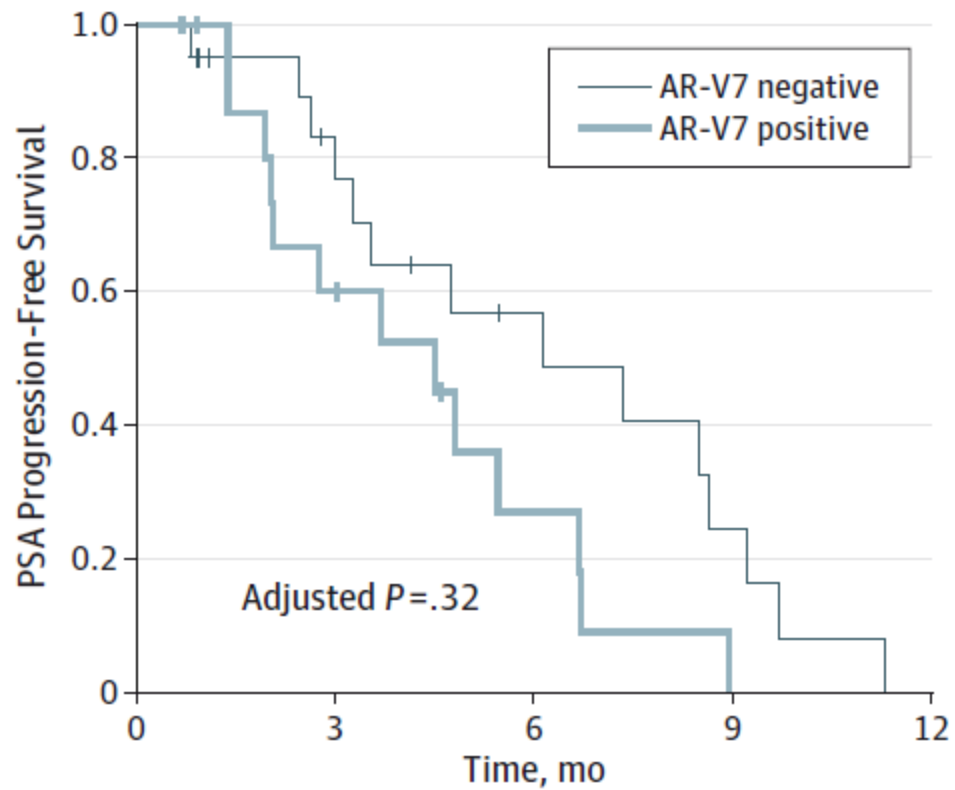
**No. at Risk**

AR-V7 negative	25	11	5	0
AR-V7 positive	6	2	0	0





**B** PSA progression-free survival



No. at risk

AR-V7 Negative	20	12	7	3	0
AR-V7 Positive	17	9	3	0	0

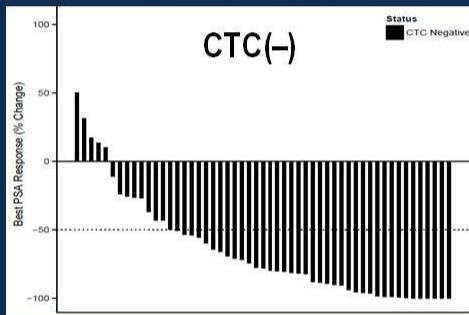


# Updated JHU Analysis (N=202)

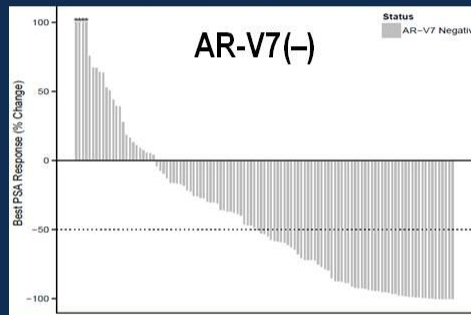
P < 0.001

Antonarakis ES et al. ASCO 2016; abstract 5012

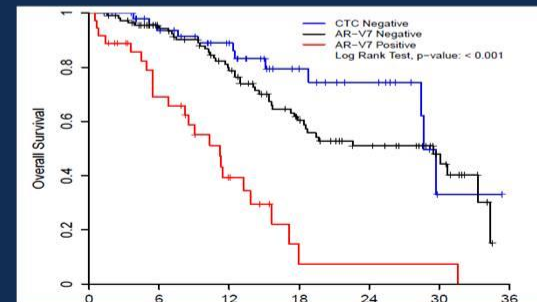
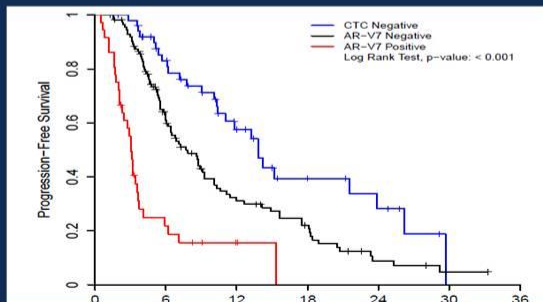
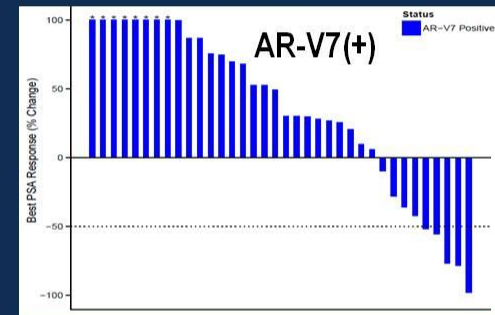
40/53 = 76%



59/113 = 52%



5/36 = 14%



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Presented by: **Emmanuel S. Antonarakis, M.D.**

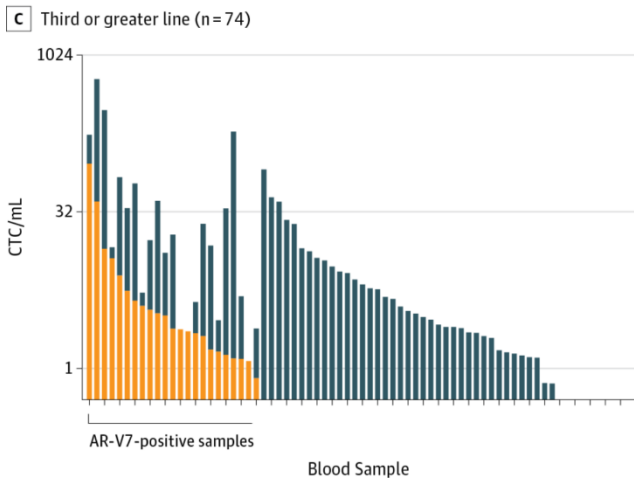
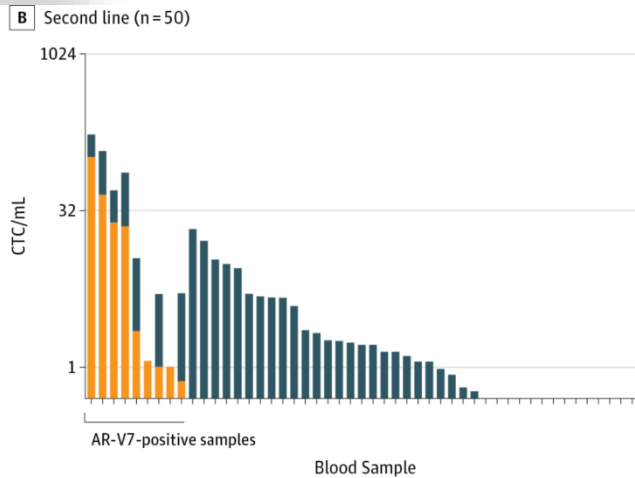
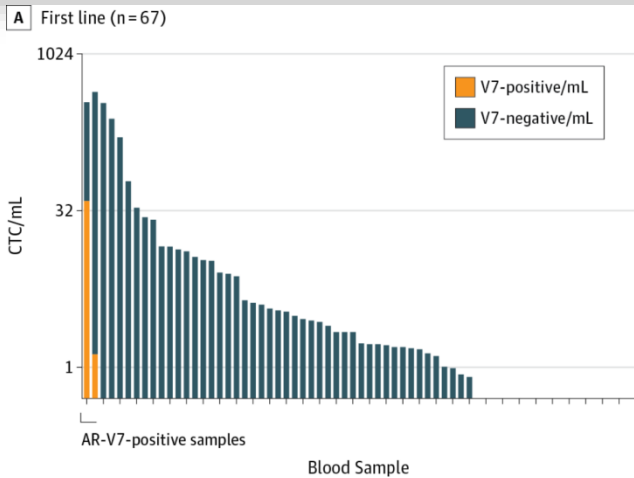


Original Investigation

# Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer

Howard I. Scher, MD; David Lu, PhD; Nicole A. Schreiber, BA; Jessica Louw, BS; Ryon P. Graf, PhD; Hebert A. Vargas, MD; Ann Johnson, MS; Adam Jendrisak, MBA; Richard Bambury, MB, BCh, BAO; Daniel Danila, MD; Brigit McLaughlin, BS; Justin Wahl, BS; Stephanie B. Greene, PhD; Glenn Heller, PhD; Dena Marrinucci, PhD; Martin Fleisher, PhD; Ryan Dittamore, MBA

*JAMA Oncol.* doi:10.1001/jamaoncol.2016.1828  
Published online June 4, 2016.



**D** Incidence and subclonal contribution of AR-V7-positive CTCs by line of therapy

Line of Tx in mCRPC setting (n samples)	First (n = 67)	Second (n = 50)	Third or greater (n = 74)
Samples with AR-V7-positive CTCs	2 (3%)	9 (18%)	23 (31%)
AR-V7-positive CTCs in samples with AR-V7-positive CTCs, %, median (range)	5.7% (0.3%-11.2%)	38% (14.3%-100%)	21% (0.5%-100%)

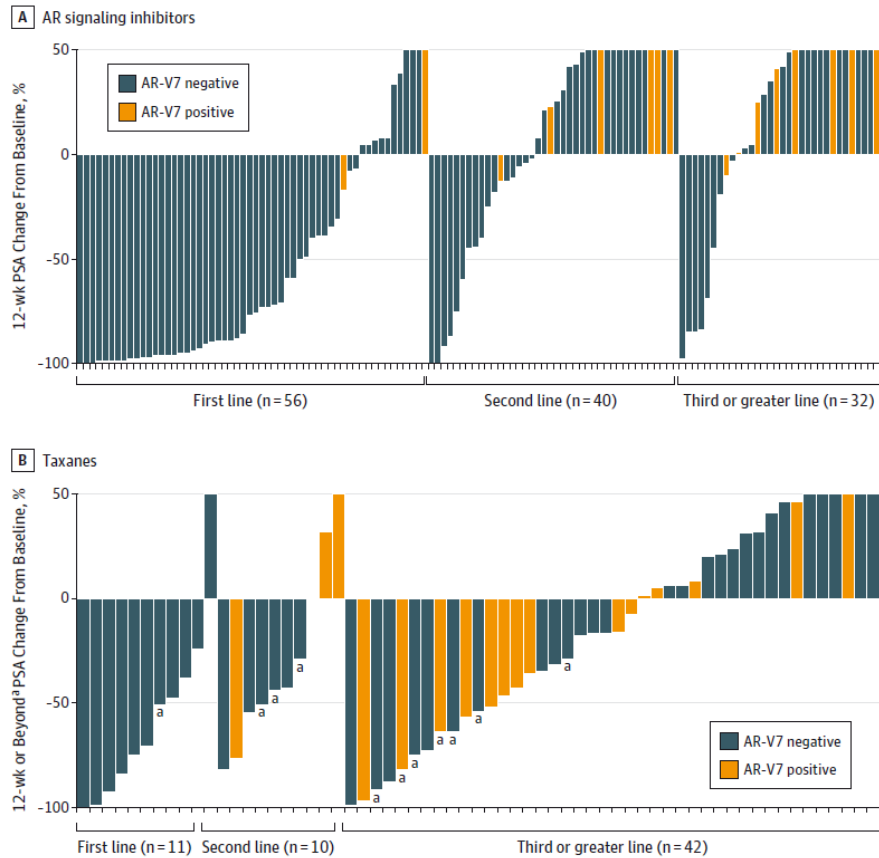


Original Investigation

# Association of AR-V7 on Circulating Tumor Cells as a Treatment-Specific Biomarker With Outcomes and Survival in Castration-Resistant Prostate Cancer

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*JAMA Oncol.* doi:10.1001/jamaoncol.2016.1828  
Published online June 4, 2016.



Original Investigation

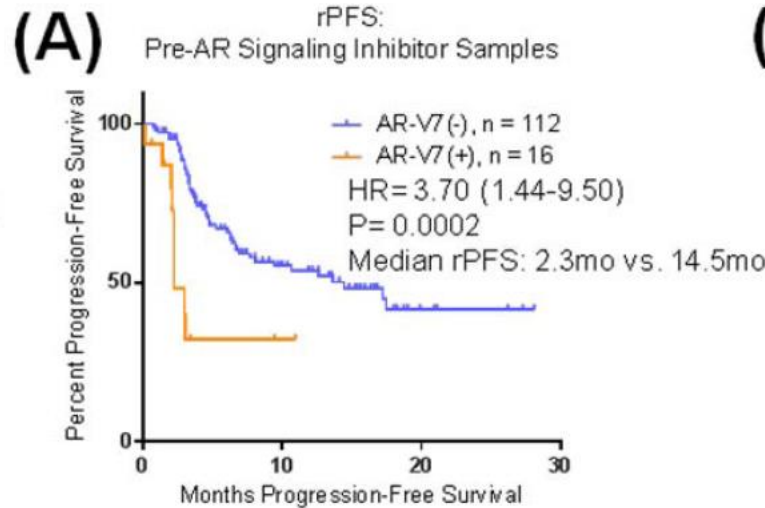
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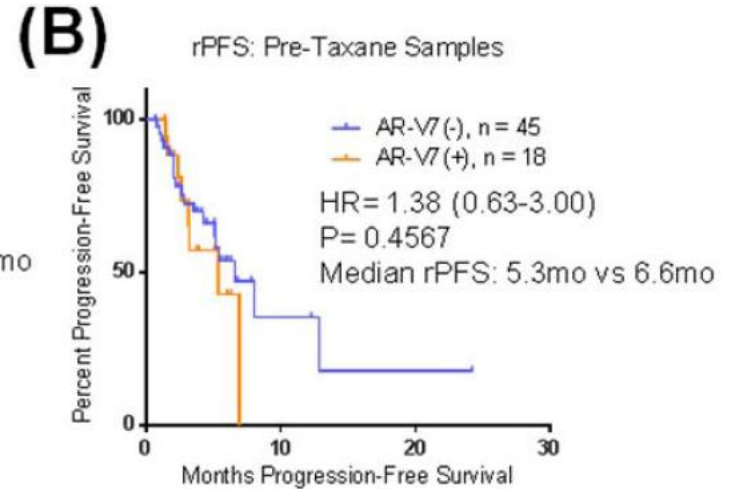
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## Progression-Free Survival

### AR Signaling Inhibitors



### Taxanes

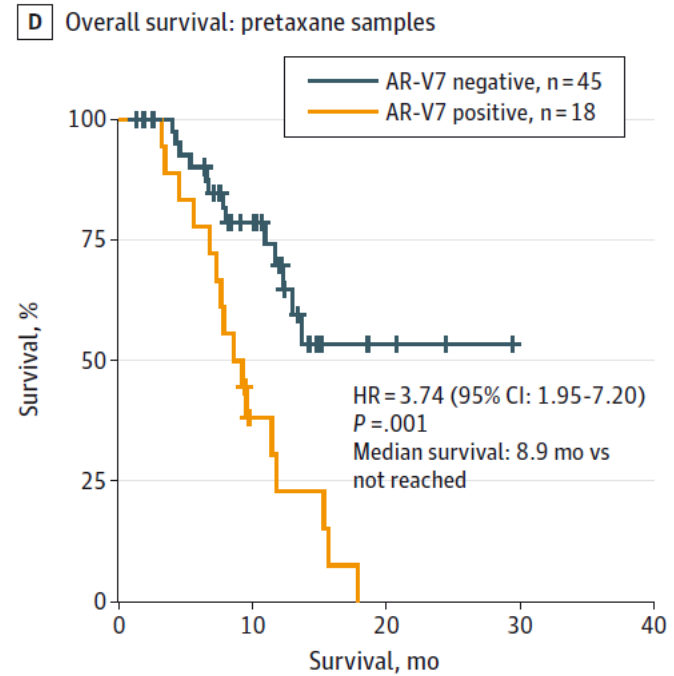
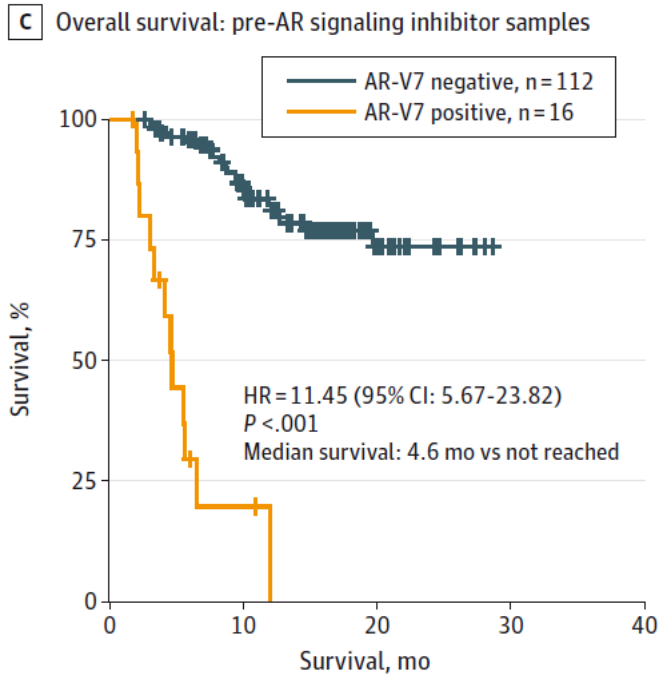


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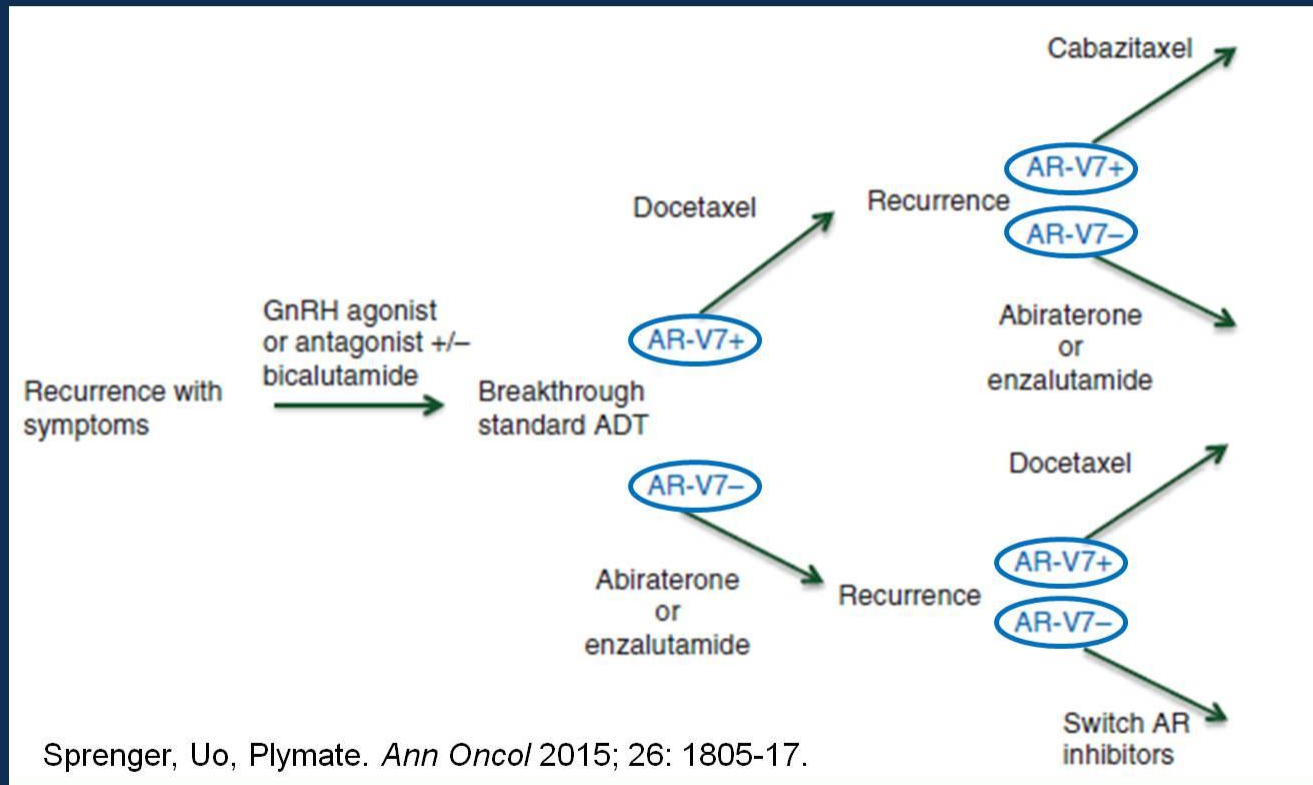
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# Decision Schema



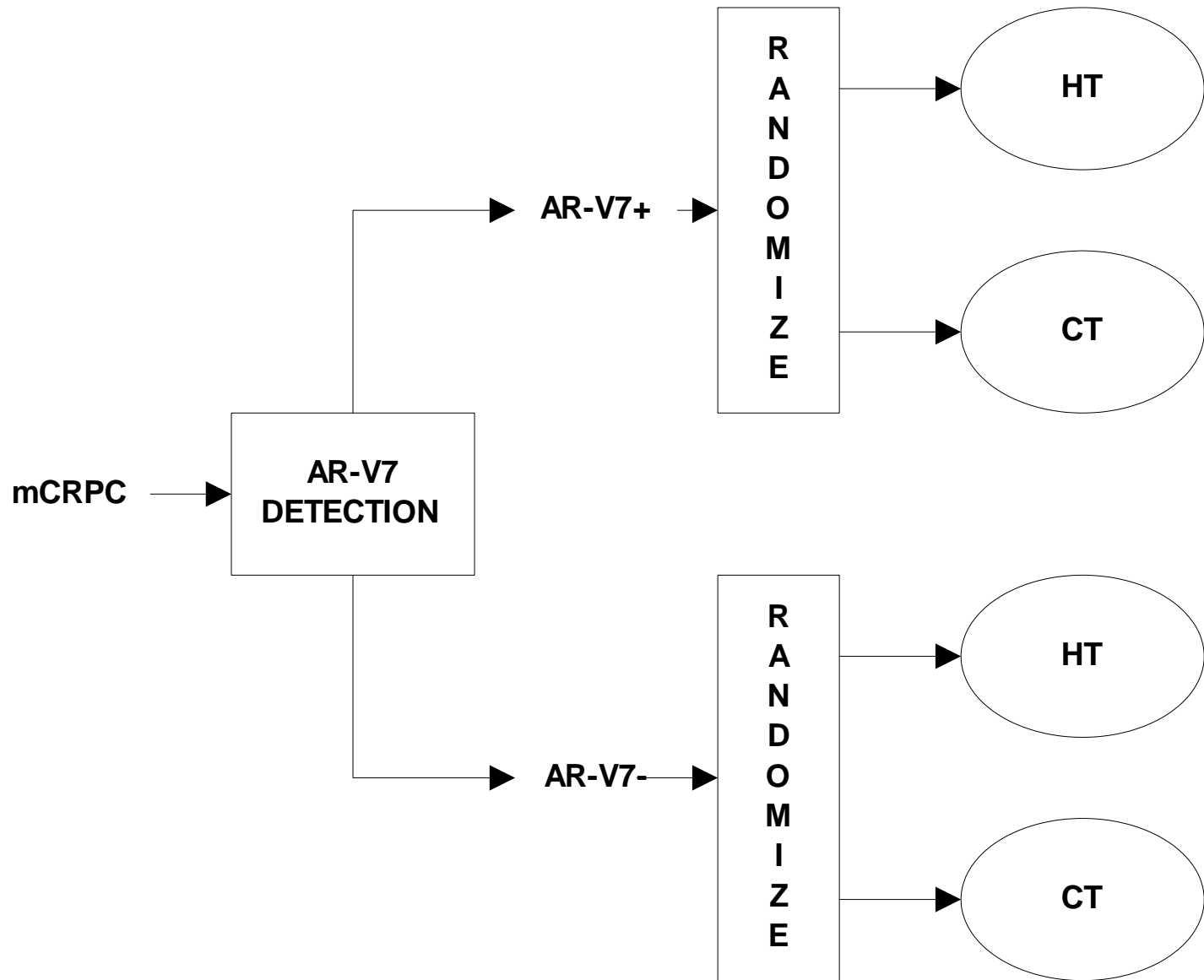
Sprenger, Uo, Plymate. *Ann Oncol* 2015; 26: 1805-17.

PRESENTED AT: **ASCO ANNUAL MEETING '16**

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Presented by: **Emmanuel S. Antonarakis, M.D.**







# 2016 landscape

**LOCAL TREATS**

**BIOCHEMICAL RELAPSE**

**METASTASES**

**ADT**

**AntiAndrogens**

**HSPC**

**CRPC**

**Docetaxel**

**Abiraterone**

**Enzalutamide**

**Docetaxel**

**Cabazitaxel**

**Enzalutamide**

**Abiraterone**

**Ra 223**



# New agents mechanism of action

**CYP17**



**MIT**



**RA223**



# New agents mechanism of action

**CYP17**



**MIT**



**$\alpha$ -MEDIATED  
DNA DAMAGE**



# AROUND THE CORNER





# The NEW ENGLAND JOURNAL of MEDICINE

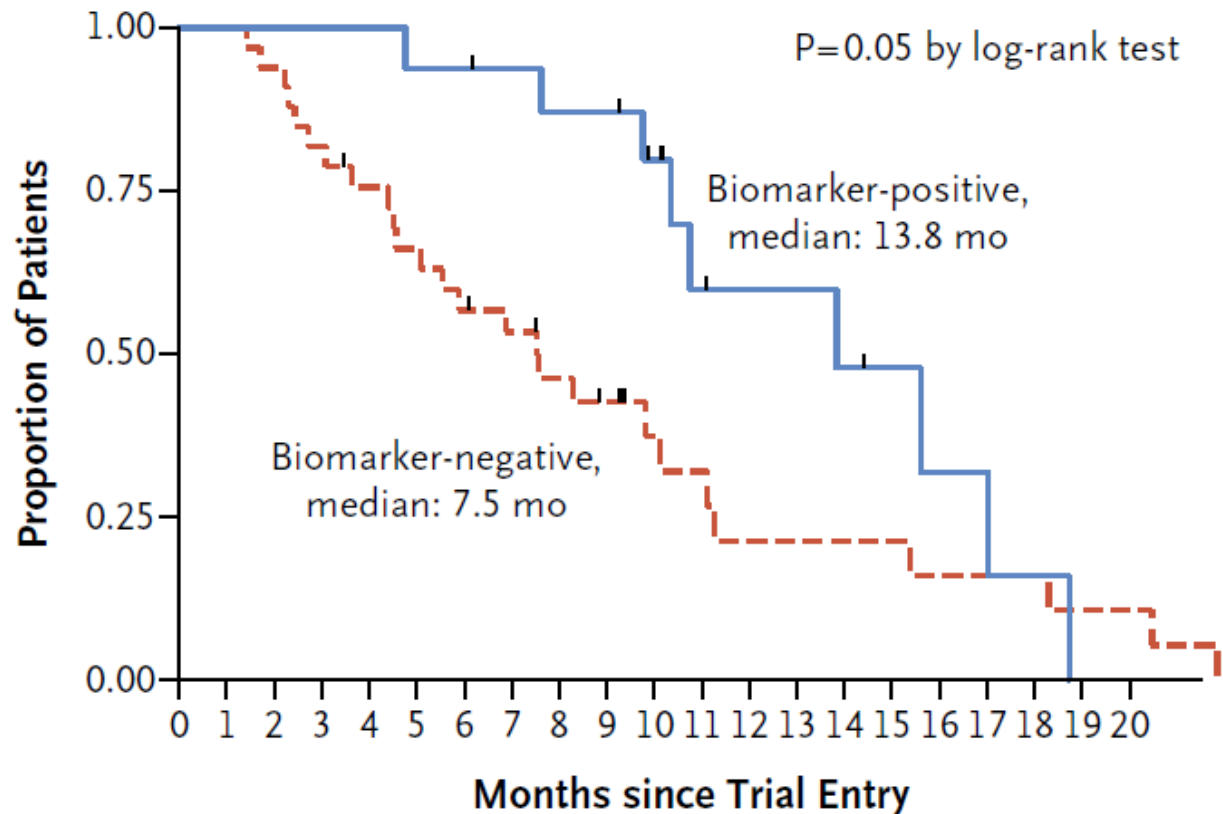
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## DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

### Overall Survival



# Clinical trial strategies

Trial	Phase	Population	Agent
NCT01682772 TOPARP	II	mCRPC post-doce Unselected Most were post-abi/enza post-doce	Olaparib (Mateo, NEJM, 2016)
NCT01085422	II	mCRPC, post-doce, unselected At least 1 but not more than 2 therapies	Veliparib + TMZ (Hussain, Inv New Drugs, 2014)
NCT01576172	II	mCRPC, abi/enza naive, unselected	Abi +/- veliparib (Hussain, ASCO 2016)
NCT01972217	II	mCRPC post-doce, unselected	Abi +/- olaparib
NCT02500901	I	mCRPC broad eligibility, unselected	Enza + niraparib
NCT02324998	I	Pre-RRP int/high risk, unselected	Degarelix + olaparib

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**THANK YOU**

