

Con il patrocinio di



## ONCOLOGIA AL FEMMINILE 2015

*Un filo sottile per coniugare  
i progressi scientifici con la  
pratica clinica, le linee guida e l'etica*

Coordinatore Scientifico  
Stefania Gori



VERONA, Hotel Leon d'Oro - 18/19 Settembre 2015

# Il carcinoma prostatico metastatico: Quale prima linea? Quale terapia nelle linee successive?

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S.C. di Oncologia  
Terni*

# ***METASTATIC PROSTATE CANCER***

## **DIFFERENT THERAPEUTIC APPROACHES**

- ✓ Metastatic Hormone-sensitive Disease
- ✓ Asymptomatic or mildly symptomatic Metastatic CRPC
- ✓ Symptomatic Chemotherapy-naïve Metastatic CRPC
- ✓ Post-Docetaxel Metastatic CRPC

***METASTATIC HORMONE-SENSITIVE DISEASE***

# *THE NATURAL HISTORY OF METASTATIC PROSTATE CANCER*

**ADT**

**Docetaxel, Cabazitaxel,  
Enzalutamide, Abiraterone,  
Radium-223**

**M1 HSPC**

**M1 HSPC under control**

**CRPC**

**Death**



**Time (median: 4-5 years)**

# ***METASTATIC HORMONE-SENSITIVE DISEASE***

Hypothesis of CHAARTED, GETUG 15, STAMPEDE trials:

- Early docetaxel will postpone progression to CRPC and death

M1 HSPC



M1 HSPC under control

CRPC

Death



Time to progression



Time to death

***WHAT ARE WE TALKING ABOUT?***

# ***METASTATIC HORMONE-SENSITIVE DISEASE***

Localized prostate cancer  
→ PSA failure

**44% of deaths**

Metastatic Hormone-naïve  
Prostate cancer

De novo metastatic  
prostate cancer

**56% of deaths**

# ***METASTATIC HORMONE-SENSITIVE DISEASE***

Localized prostate cancer  
→ PSA failure

**Scenario 1:**  
**27% in CHAARTED**  
**28% in GETUG 15**  
**29% in STAMPEDE**

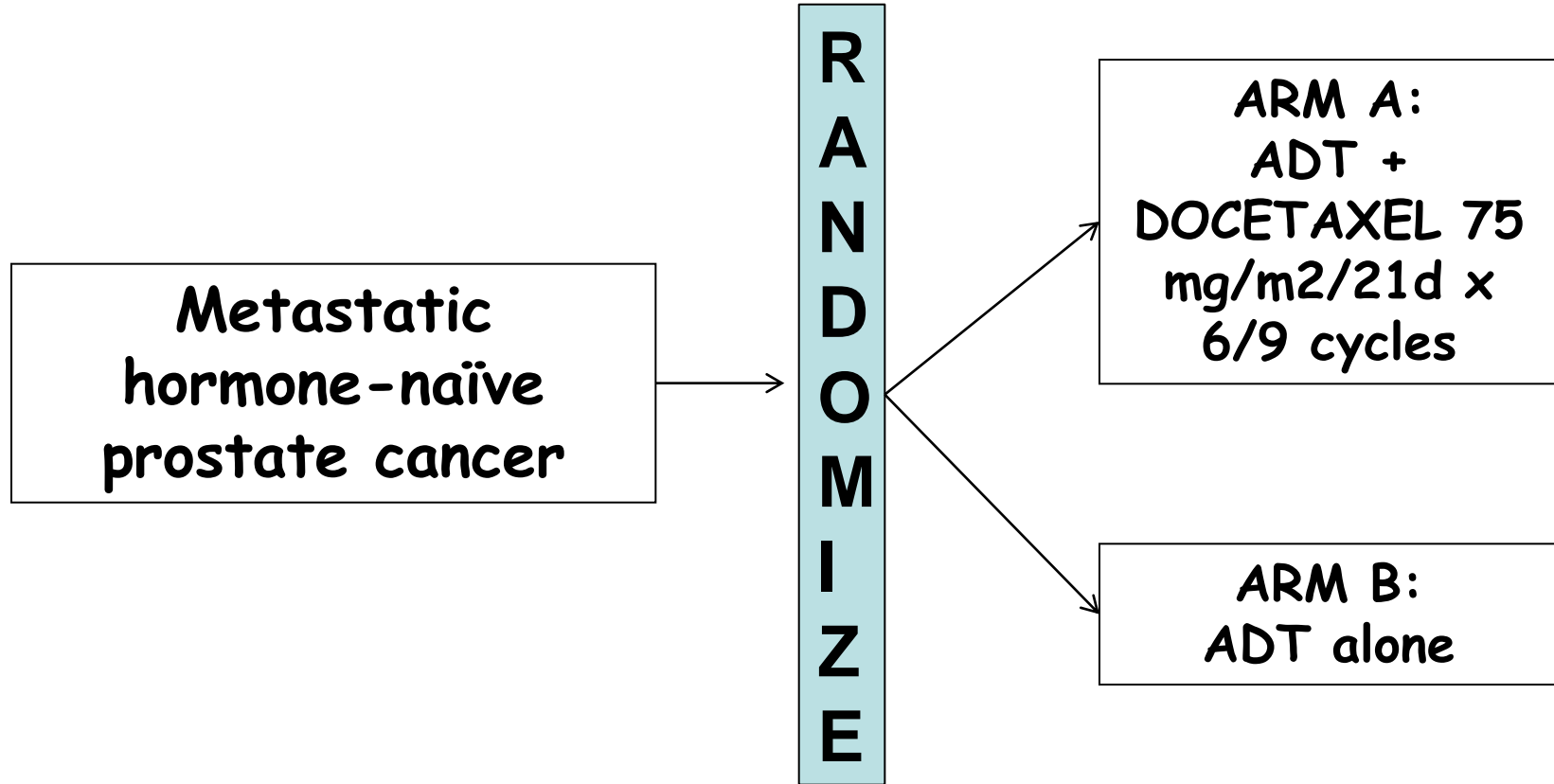
Metastatic Hormone-naïve  
Prostate cancer

De novo metastatic  
prostate cancer

**Scenario 2:**  
**73% in CHAARTED**  
**72% in GETUG 15**  
**71% in STAMPEDE**

# ***METASTATIC HORMONE-SENSITIVE DISEASE***

## **CHAARTED and GETUG 15**

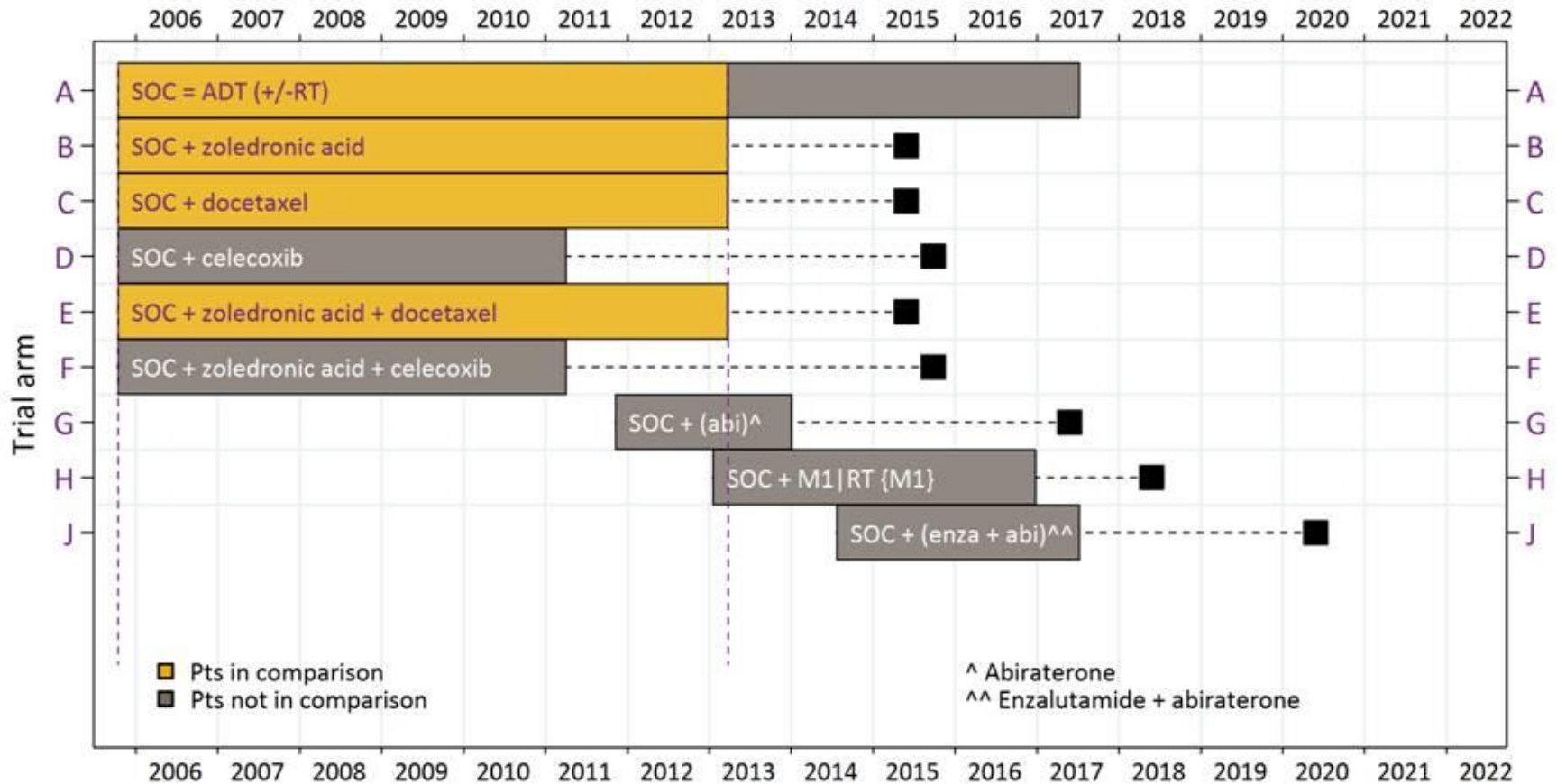


**Primary endpoint: OS**

# METASTATIC HORMONE-SENSITIVE DISEASE

## STAMPEDE

STAMPEDE: All docetaxel and zoledronic acid comparisons



A = ~1200 pts --> ~404 primary outcome measure events

B = ~600 pts, C = ~600 pts, E = ~600 pts

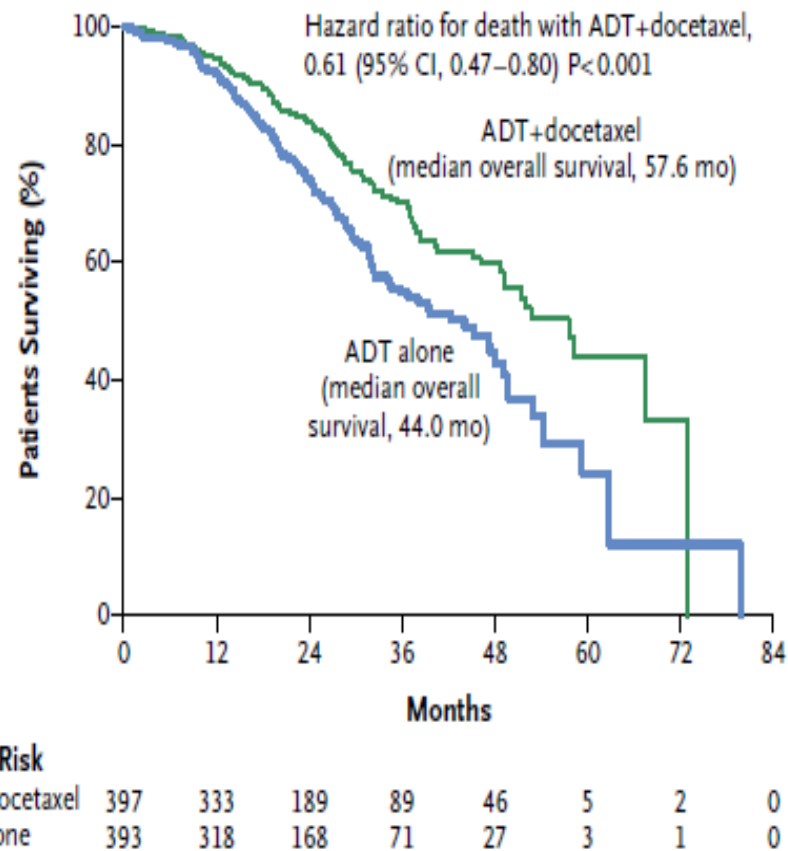
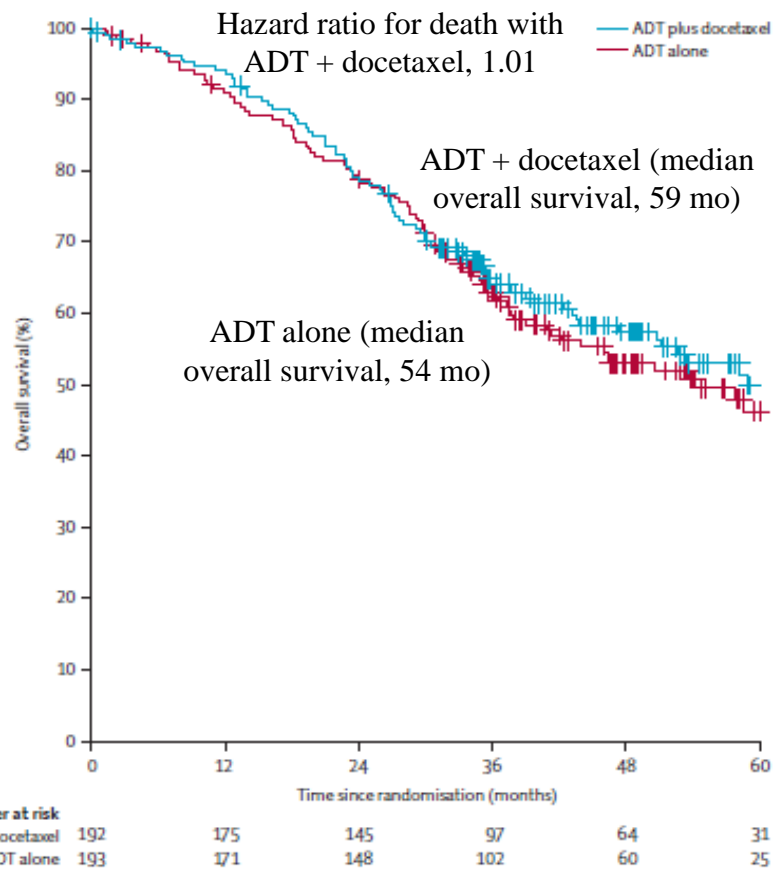
## ***METASTATIC HORMONE-SENSITIVE DISEASE***

| Presenting features       | CHAARTED                              | GETUG 15                              | STAMPEDE                               |
|---------------------------|---------------------------------------|---------------------------------------|--|
| Number                    | 790                                   | 385                                   | 2962 (61% M1)                          |
| Geography                 | N.America                             | France/Belgium                        | UK/Switzerland                         |
| Recruitment period        | 2006-2012                             | 2004-2008                             | 2005-2013                              |
| Follow-up                 | 29 months                             | 50 months                             | NR                                     |
| Age                       | 64 years                              | 64 years                              | 65 years                               |
| High volume of metastases | 65%                                   | 47.5%                                 | Unknown                                |
| PSA at entry              | 53 ng/ml                              | 26 ng/ml                              | NR                                     |
| <b>Outcomes</b>           |                                       |                                       |  |
| Improved PSA/clinical PFS | 20.7m vs 14.7m<br>HR 0.56 (0.44-0.70) | 22.9m vs 12.9m<br>HR 0.72 (0.57-0.91) | FFS: 37m vs 21m<br>HR=0.62 (0.54-0.70) |

# METASTATIC HORMONE-SENSITIVE DISEASE

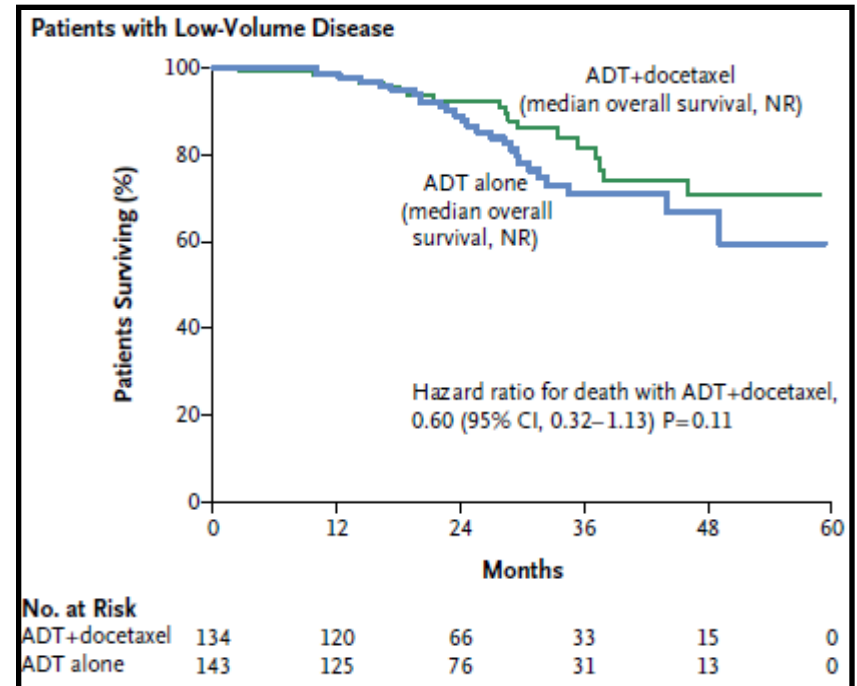
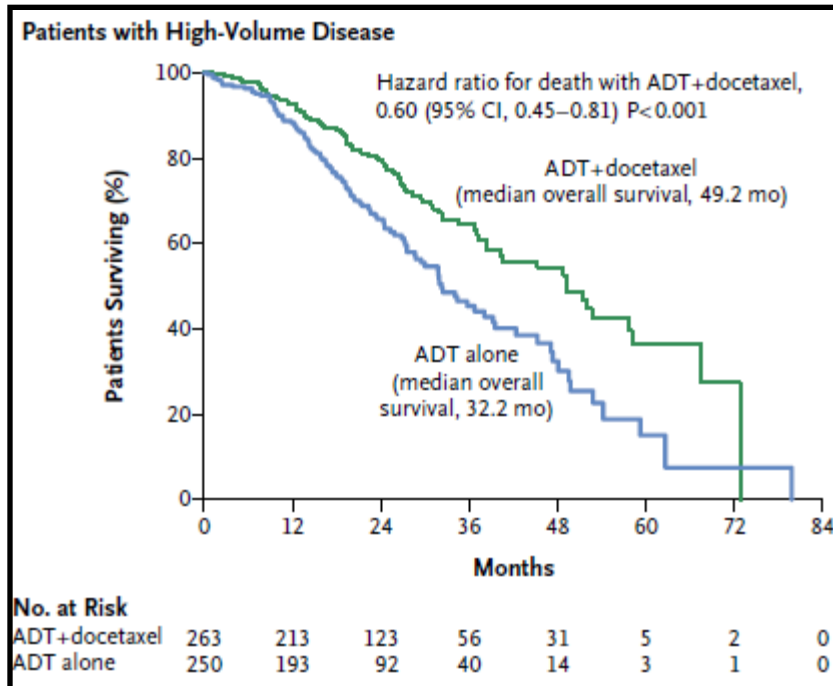
## GETUG 15

## CHAARTED



# METASTATIC HORMONE-SENSITIVE DISEASE

## CHAARTED

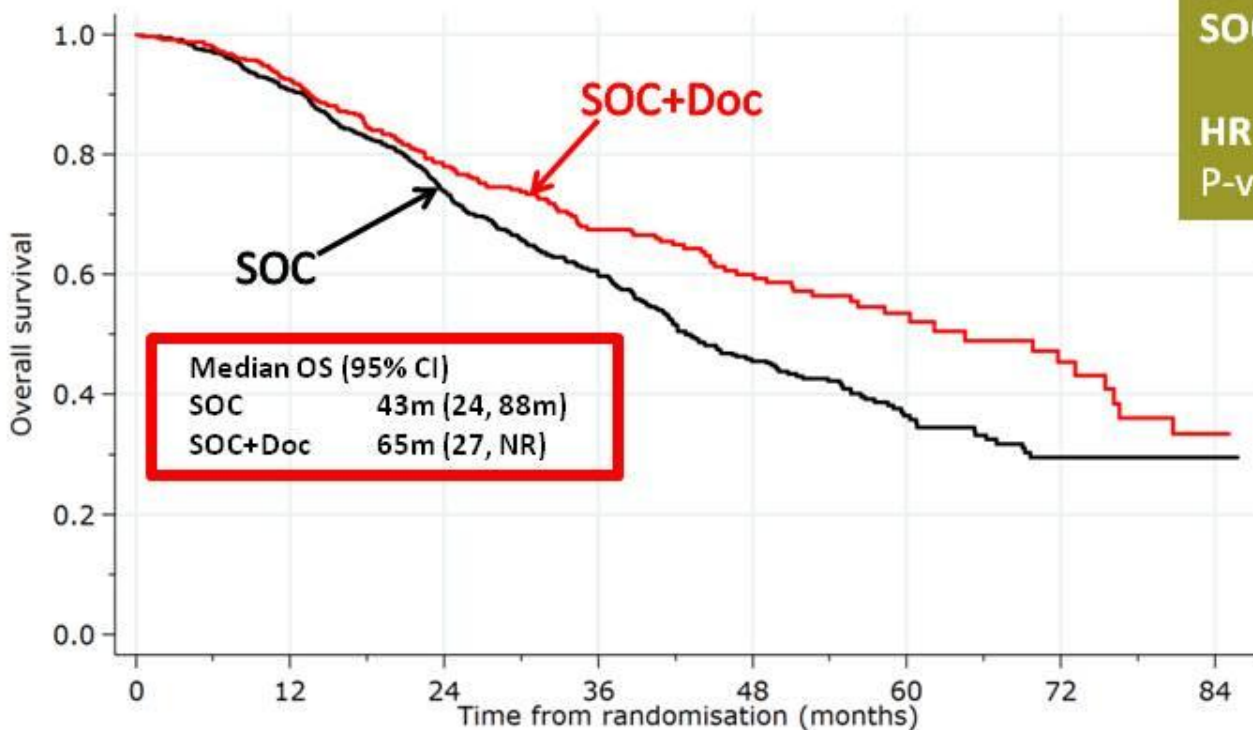


**GETUG 15: No differences in OS in high or low volume disease**

# METASTATIC HORMONE-SENSITIVE DISEASE

## STAMPEDE

### Docetaxel: Survival – M1 Patients



|            |                   |
|------------|-------------------|
| SOC        | 343 deaths        |
| SOC+Doc    | 134 deaths        |
| HR (95%CI) | 0.73 (0.59, 0.89) |
| P-value    | 0.002             |

Non-PH p-value 0.23

| Restricted mean OS time |                   |
|-------------------------|-------------------|
| SOC                     | 49.3m             |
| SOC+Doc                 | 56.1m             |
| Diff (95%CI)            | 6.8m (2.8, 11.0m) |

Group  
At risk (events)

|         |     |      |     |       |     |      |     |      |     |      |    |      |    |     |    |
|---------|-----|------|-----|-------|-----|------|-----|------|-----|------|----|------|----|-----|----|
| SOC     | 725 | (66) | 645 | (117) | 469 | (75) | 254 | (52) | 134 | (21) | 58 | (10) | 24 | (0) | 10 |
| SOC+Doc | 362 | (27) | 326 | (49)  | 242 | (27) | 151 | (13) | 91  | (8)  | 37 | (5)  | 24 | (5) | 9  |

## ***METASTATIC HORMONE-SENSITIVE DISEASE***

|             | CHAAR<br>TED | CHAAR<br>TED | GETUG<br>15 | GETUG<br>15 | STAMPE<br>DE | STAMPE<br>DE |
|-------------|--------------|--------------|-------------|-------------|--------------|--------------|
|             | ADT+ D       | ADT          | ADT+ D      | ADT         | ADT+ D       | ADT          |
| Docetaxel   | 12.4%        | 33%          | 45%         | 80%         | 14%          | 41%          |
| Cabazitaxel | 11%          | 7%           | 2%          | 1%          | 6%           | 3%           |
| Abi/Enza    | 23%          | 20%          | 15%         | 15%         | 35%          | 30%          |

- **"Salvage" docetaxel much more frequent in GETUG 15**
  - **GETUG 15 is underpowered in high volume disease**

# ***METASTATIC HORMONE-SENSITIVE DISEASE***



## **RECOMMENDATION #1**

Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, **should be offered 6 cycles of docetaxel in addition to ADT**

***METASTATIC CASTRATION-RESISTANT PROSTATE CANCER***

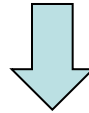
# *QUESTIONS CONCERNING TREATMENT CHOICE IN METASTATIC CRPC*

- **Selecting the right treatment for a specific patient**
- **Optimal sequencing of available agents**
- *Combination therapy prospects*

***ASYMPTOMATIC OR MILDLY SYMPTOMATIC  
METASTATIC CRPC***

*ASYMPTOMATIC OR MILDLY SYMPTOMATIC  
METASTATIC CRPC*

**Standard Treatment**



**ABIRATERONE**

**ENZALUTAMIDE**

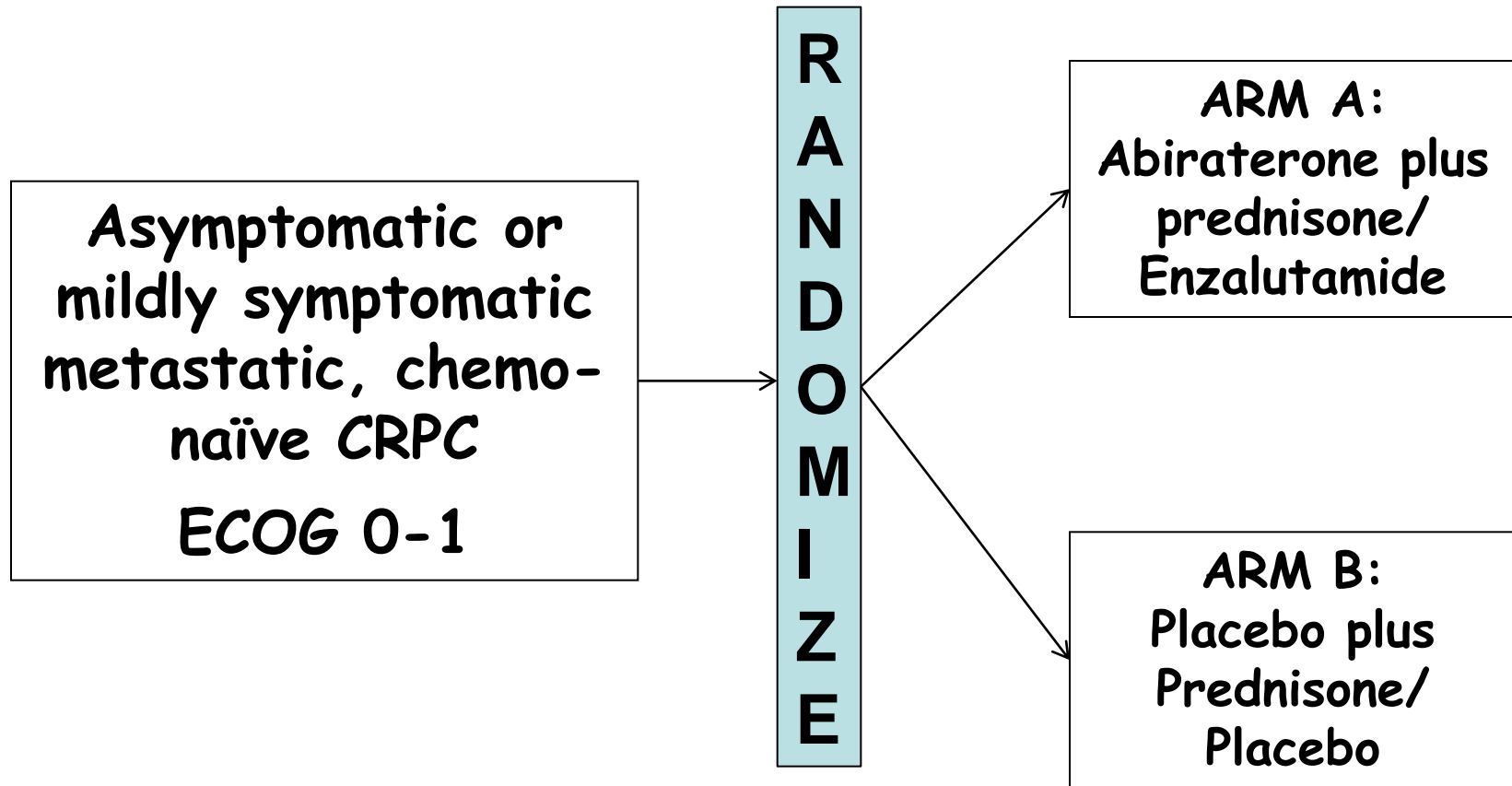
*SIPULEUCEL-T*

*DOCETAXEL*

*ASYMPTOMATIC OR MILDLY SYMPTOMATIC*

*METASTATIC CRPC*

**COU-AA-302 and PREVAIL**



**Coprimary endpoints: OS and radiographic PFS**

# *ASYMPTOMATIC OR MILDLY SYMPTOMATIC*

## *METASTATIC CRPC*

| Presenting features  | COU-AA-302<br>(ABI) | PREVAIL<br>(ENZA) |
|--|---------------------|-------------------|
| Number   | 1088                | 1717              |
| Age  | 70.5                | 71                |
| PSA at entry   | 40 ng/ml            | 49 ng/ml          |
| Time from initial diagnosis or first treatment of prostate cancer to randomization | 63 months           | 63 months         |
| Distribution of disease at screening   |                     |                   |
| Bone only  | 50%                 | 40%               |
| Lymph node   | 49.5%               | 50.5%             |
| Visceral disease   | 0.7%                | 11.5%             |

# *ASYMPTOMATIC OR MILDLY SYMPTOMATIC*

## *METASTATIC CRPC*

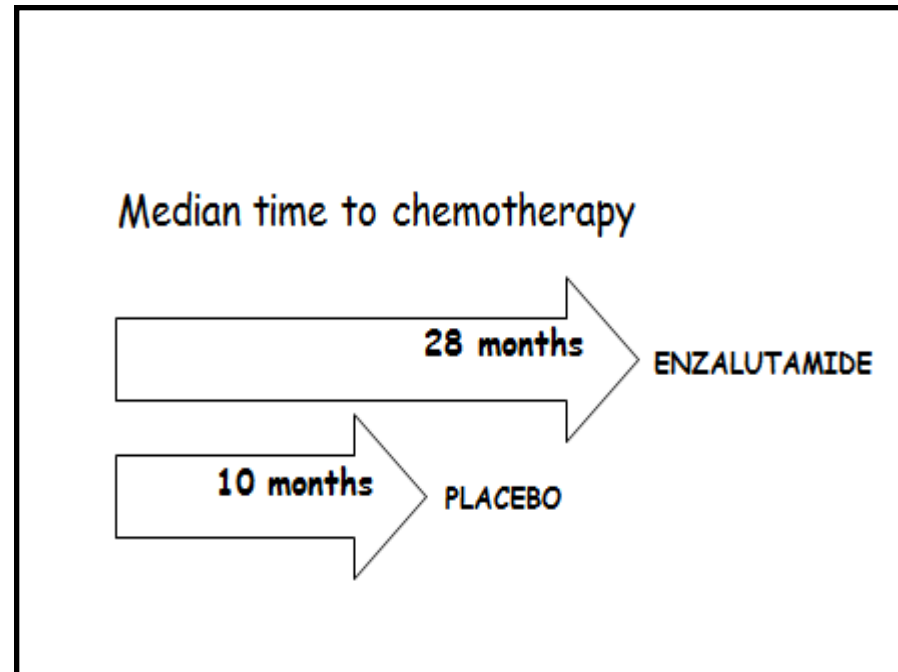
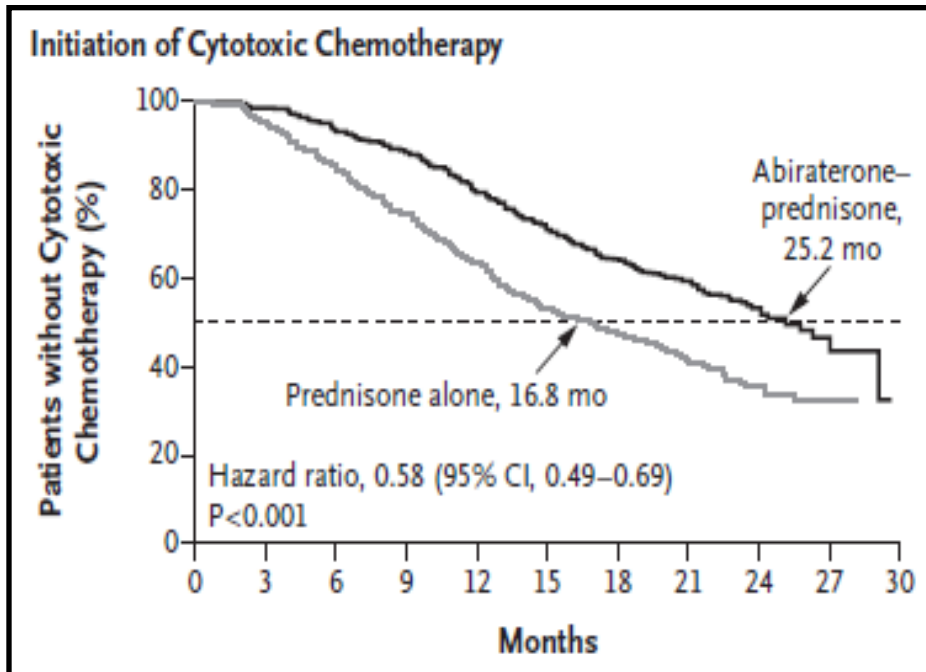
| <b>TRIAL</b>                                       | <b>N.<br/>pts</b> | <b>OS<br/>(months)</b>                | <b>rPFS<br/>(months)</b>            |
|--|-------------------|---------------------------------------|-------------------------------------|
| Abiraterone/Prednisone<br>vs<br>Placebo/Prednisone | 1088              | 34.7 vs 30.3<br>HR 0.81<br>(p=0.0033) | 16.5 vs 8.3<br>HR 0.53<br>(p<0.001) |
| Enzalutamide<br>vs<br>placebo                      | 1717              | 35.3 vs 31.3<br>HR 0.71<br>(p<0.0001) | NR vs 3.9<br>HR 0.19<br>(p<0.0001)  |

***ASYMPTOMATIC OR MILDLY SYMPTOMATIC  
METASTATIC CRPC***

|              | COU-AA-302 | COU-AA-302 | PREVAIL | PREVAIL |
|--------------|------------|------------|---------|---------|
|              | ABI        | PLACEBO    | ENZA    | PLACEBO |
| Docetaxel    | 38%        | 53%        | 32.8%   | 56.7%   |
| Cabazitaxel  | 8%         | 10%        | 5.8%    | 13.0%   |
| Abiraterone  | 5%         | 10%        | 20.5%   | 45.6%   |
| Enzalutamide | NR         | NR         | 1.0%    | 4.4%    |

# *ASYMPTOMATIC OR MILDLY SYMPTOMATIC METASTATIC CRPC*

- Abiraterone and Enzalutamide significantly delayed time to chemotherapy

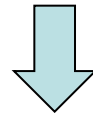


*SYMPTOMATIC*

*CHEMOTHERAPY-NAÏVE METASTATIC CRPC*

# *SYMPTOMATIC CHEMO-NAÏVE METASTATIC CRPC*

## Standard Treatment



**DOCETAXEL 75 mg/mq q21 + Prednisone 5 mg bid**

**RADIUM-223 50kBq/kg q28 for symptomatic bone metastases, without visceral metastases**

# SYMPTOMATIC CHEMO-NAÏVE METASTATIC CRPC

## TAX 327: Study Design

### Stratification:

Pain level  
PPI  $\geq 2$  or AS  $\geq 10$   
vs  
PPI  $< 2$  or AS  $< 10$

KPS  
 $\leq 70$  vs  $\geq 80$

R  
A  
N  
D  
O  
M  
I  
Z  
E

Docetaxel 75 mg/m<sup>2</sup> q 3 wk +  
Prednisone 5 mg bid

Docetaxel 30 mg/m<sup>2</sup> wkly  
5 of 6 wks +  
Prednisone 5 mg bid

Mitoxantrone 12 mg/m<sup>2</sup>  
q 3 wk +  
Prednisone 5 mg bid

Treatment duration in all 3 arms = 30 wks

Eisenberger et al. *Proc ASCO*. 2004;23:2. Abstract 4.

Overall more than  
1.600 met HRPC pts  
treated

Docetaxel improves OS  
and TTP in advanced  
hormone-refractory  
prostate cancer patients

## SWOG 9916: Study Design

D/E\*

Docetaxel 60 mg/m<sup>2</sup> IV D2 every 21 days  
Estramustine 280 mg po TID, D1-5

Premedication: Dexamethasone 20 mg PO TID starting evening of D1

R

M/P

Mitoxantrone 12 mg/m<sup>2</sup> IV every 21 days  
Prednisone 5 mg po BID continuously

\*Per protocol amendment January 15, 2001: Coumadin 2 mg PO daily +  
ASA 325 mg PO daily was added.  
Docetaxel and mitoxantrone doses could be increased to 70 mg/m<sup>2</sup> and  
14 mg/m<sup>2</sup>, respectively, if no grade 3 or 4 toxicities were seen in cycle 1.

Petrylak et al. *Proc ASCO*. 2004;23:2. Abstract 3.

# SYMPTOMATIC CHEMO-NAÏVE METASTATIC CRPC

## The NEW ENGLAND JOURNAL of MEDICINE

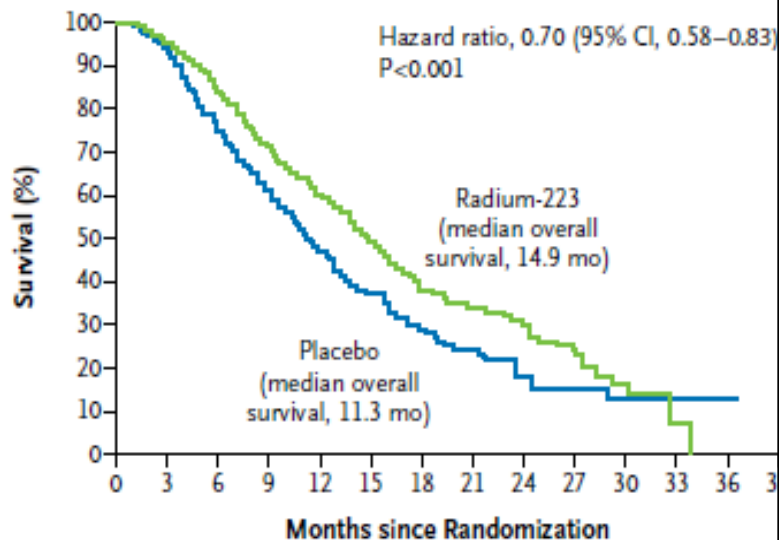
ESTABLISHED IN 1812

JULY 18, 2013

VOL. 369 NO. 3

### Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

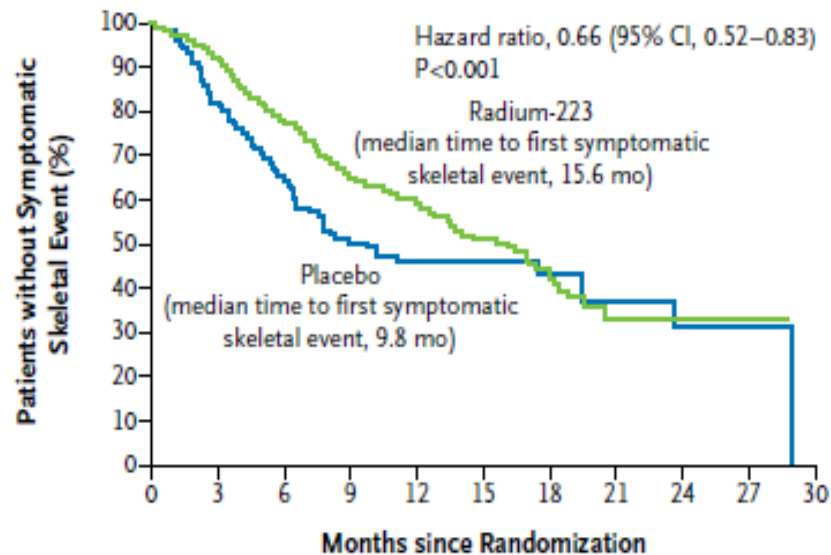
**A Overall Survival**



No. at Risk

|            |     |     |     |     |     |     |     |    |    |    |   |   |   |
|------------|-----|-----|-----|-----|-----|-----|-----|----|----|----|---|---|---|
| Radium-223 | 614 | 578 | 504 | 369 | 274 | 178 | 105 | 60 | 41 | 18 | 7 | 1 | 0 |
| Placebo    | 307 | 288 | 228 | 157 | 103 | 67  | 39  | 24 | 14 | 7  | 4 | 2 | 1 |

**B Time to First Symptomatic Skeletal Event**



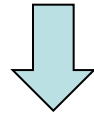
No. at Risk

|            |     |     |     |     |     |    |    |   |   |   |   |
|------------|-----|-----|-----|-----|-----|----|----|---|---|---|---|
| Radium-223 | 614 | 496 | 342 | 199 | 129 | 63 | 31 | 8 | 8 | 1 | 0 |
| Placebo    | 307 | 211 | 117 | 56  | 36  | 20 | 9  | 7 | 4 | 1 | 0 |

***POST-DOCETAXEL METASTATIC CRPC***

# *POST-DOCETAXEL METASTATIC CRPC*

## Standard Treatment



**ABIRATERONE**

**ENZALUTAMIDE**

**CABAZITAXEL**

**RADIUM-223**

## *POST-DOCETAXEL METASTATIC CRPC*

| <b>TRIAL</b>                      | <b>N. pts</b> | <b>OS (months)</b>         | <b>Radiographic PFS (months)</b>   |
|-----------------------------------|---------------|----------------------------|--|
| Abiraterone<br>vs<br>placebo      | 1195          | 15.8 vs 11.2<br>(p<0.0001) | 5.6 vs 3.6<br>(p<0.0001)   |
| Enzalutamide<br>vs<br>placebo     | 1199          | 18.4 vs 13.6<br>(p<0.001)  | 8.3 vs 2.9<br>(p<0.001)  |
| Cabazitaxel<br>vs<br>Mitoxantrone | 755           | 15.1 vs 12.7<br>(p<0.0001) | 2.8 vs 1.4<br>(p<0.0001)   |
| Radium-223<br>vs<br>placebo       | 921           | 14.9 vs 11.3<br>(p=0.001)  | Time to the first<br>symptomatic skeletal<br>event<br>15.6 vs 9.8<br>(p<0.001) |

## ***METASTATIC PROSTATE CANCER: CONCLUSIONS***

- Placebo-controlled trials may no longer be ethical or feasible in men with mCRPC
- Is it still realistic to demand that new agents increase OS among patients with metastatic castration-resistant prostate cancer?
- None of these new therapies have been directly compared to each other
- No prospective sequencing trials
- Is there cross resistance among therapies?

## ***METASTATIC PROSTATE CANCER: CONCLUSIONS***

- **Selection of the patients who will be responsive could significantly improve the outcomes**
- **Clinical, radiologic, biologic and genomic predictive biomarkers should be identified and validated**

### **ORIGINAL ARTICLE**

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

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D.,  
Brandon Lubber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S.,  
Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D.,  
Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D.,  
Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D.,  
Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D.,  
Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

# *PROPOSED TREATMENT PARADIGM OF mCRPC*

## **SCENARIO 1:**

M1 at diagnosis or short response to ADT mCRPC

ADT

DOCETAXEL

CABAZITAXEL

ABI/ENZA

## **SCENARIO 2:**

Asymptomatic or mildly symptomatic mCRPC

ADT

ABI

DOCETAXEL

ENZA

CABAZITAXEL

## **SCENARIO 3:**

Symptomatic mCRPC

ADT

DOCETAXEL

ABI/ENZA

CABAZITAXEL

# *PROPOSED TREATMENT PARADIGM OF mCRPC*

## **SCENARIO 1:** Symptomatic mCRPC



## **SCENARIO 2:** Mildly symptomatic mCRPC



## **SCENARIO 3:** Post-docetaxel mCRPC



# ***METASTATIC PROSTATE CANCER***

