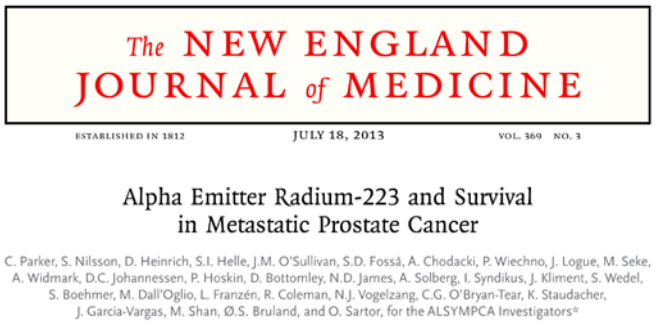
# SVILUPPI FUTURI E TAKE HOME MESSAGES

**Prof. G.Cartenì**
**Prof. E. Cortesi**



# Lo sviluppo clinico nel carcinoma della prostata

# Morris, MJ et al (Abstract 5012)
# Effects of Radium-223 dichloride (Ra-223) with docetaxel on prostate-specific antigen (PSA) and bone metastases: A Phase 1/2A Clinical Trial

## EFFECTS OF RADIUM-223 DICHLORIDE (RA-223) WITH DOCETAXEL (D) VS D ON PROSTATE-SPECIFIC ANTIGEN (PSA) AND BONE ALKALINE PHOSPHATASE (BALP) IN PATIENTS (PTS) WITH CASTRATION-RESISTANT PROSTATE CANCER (CRPC) AND BONE METASTASES (METS): A PHASE 1/2A CLINICAL TRIAL. (MORRIS ET AL. ABSTRACT 5012)

### STUDY DESIGN AND RESULTS

- A follow-up presentation to Morris et al ASCO GU 2015 (Abstract 202) on the same endpoints.

**PATIENTS N=46**

- Progressive metastatic CRPC
- ≥2 bone metastases
- >2 lung and/or liver (>2 cm) metastases were not permitted
- No symptomatic nodal disease or other primary tumors

**OBJECTIVES: Safety,** PSA, and bALP dynamics

R 2:1

- Radium-223 50KBq/kg IV 6 week x 5 + docetaxel 60 mg/m² IV q 3 week x 10 + 5 mg prednisone bid **(n=33)**
- Docetaxel 75 mg/m² IV q 3 week x 10 (option of step down to docetaxel 60 mg/m² IV) + 5 mg prednisone bid **(n=13)**

- NOTE: Only 2/13 patients who received docetaxel alone completed the approved dose of 75 mg/m². A higher percentage of patients who received docetaxel alone (54%) compared with radium-223 + docetaxel (27%), discontinued treatment.

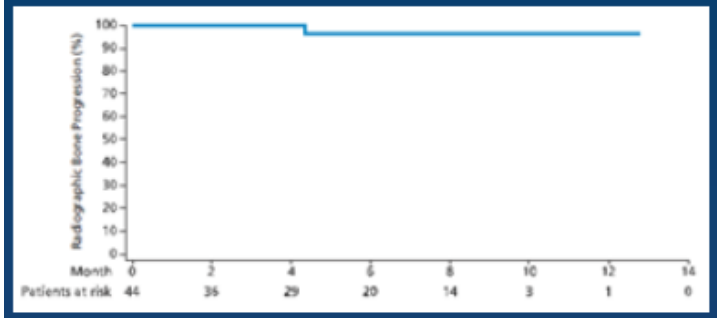
| RESULTS | PSA | | bALP* | |
|---|---|---|---|---|
| | Ra-223 + DOC (n=33) | DOC (n=13) | Ra-223 + DOC (n=23) | DOC (n=11) |
| Any increase, n (%) | 3 (9) | 4 (31) | 0 | 0 |
| Decrease, n (%) | | | | |
| <30% | 4 912) | 1 (8) | 0 | 0 |
| ≥30% | 26 (70) | 8 (62) | 23 (100) | 11 (100) |
| >50% | 20 (61) | 7 (54) | 22 (96) | 9 (82) |
| >80% | 10 (30) | 4 (31) | 9 (39) | 2(18) |
| Normalization , n (%) | N/A | N/A | 21 (91) | 7 (64) |
| Median percentage change from baseline | -75 | -55 | -77 | -59 |

ASCO GU 2015

# Sartor AO et al. Radium-223 (Ra-223) re-treatment (Re-tx): First experience from an international, multicenter, prospective study in patients (Pts) with castration-resistant prostate cancer and bone metastases (mCRPC). (3/3)

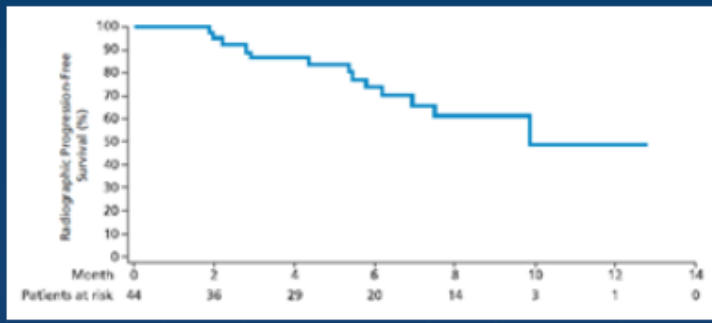
## RESULTS: Exploratory Efficacy

### Kaplan-Meier Analysis of Time to Radiographic Bone Progression




- Median time to radiographic bone progression not reached
- 1 patient confirmed radiographic bone progression

### Kaplan-Meier Analysis of Time to Radiographic Progression Free Survival




  - 2 radiographic progression from disposition but not documented in radiographic tumor assessment
  - 2 died
  - 1 confirmed radiographic bone progression
- Median time to total ALP progression not reached

**CONCLUSIONS:**

- Radiographic bone progression with Ra-223 re-treatment was rare, with the majority of disease progression occurring in soft tissue in this highly selected population
- Ra-223 re-treatment was well tolerated, with minimal hematologic toxicity, and provided continued control of disease progression in bone
- An ongoing study will address expanded Ra-223 dosing and duration of treatment

# Re-treatment Study

Abstract 197

## Radium-223 Re-treatment: First Experience From an International, Multicenter, Prospective Study in Patients With Castration-Resistant Prostate Cancer and Bone Metastases

Oliver Sartor,[1] Daniel Heinrich,[2] Neil Mariados,[3] Maria José Méndez Vidal,[4] Daniel Keizman,[5] Camilla Thellenberg-Karlsson,[6] Avivit Pe'er,[7] Giuseppe Procopio,[8] Stephen J. Frank,[9] Kalevi Pulkkanen,[10] Stefano Severi,[11] Jose Manuel Trigo Perez,[12] Paul Schwarzenberger,[13] Rui Li,[13] Luke T. Nordquist[14]

[1]Tulane Cancer Center, New Orleans, LA, USA; [2]Akershus University Hospital, Lørenskog, Norway; [3]Associated Medical Professionals of New York, PLLC, Syracuse, NY, USA; [4]Hospital Universitario Reina Sofía, Cordoba, Spain; [5]Meir Medical Center, Kfar Saba, Israel; [6]Cancercentrum Norrlands Universitetssjukhus, Umeå, Sweden; [7]Rambam Medical Center, Haifa, Israel; [8]Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; [9]Hadassah Hebrew University Medical Center, Jerusalem, Israel; [10]Kuopio University Hospital, Kuopio, Finland; [11]Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori–IRST IRCCS, Meldola, Italy; [12]Hospital Universitario Virgen de la Victoria, Málaga, Spain; [13]Bayer HealthCare, Whippany, NJ, USA; [14]GU Research Network, LLC, Omaha, NE, USA

### BACKGROUND

**Radium-223 Dichloride (Radium-223)**

- First approved alpha-emitting radiopharmaceutical with a potent and highly targeted cytotoxic effect on bone metastases[1]
- In phase 3 ALSYMPCA, radium-223 + best standard of care (BSoC) versus placebo + BSoC in patients with castration-resistant prostate cancer (CRPC) and symptomatic bone metastases[2]
  - Established efficacy with overall survival (OS) benefit; improved OS by 3.6 months (HR = 0.70; 95% CI, 0.58-0.83; $P < 0.001$)
  - Had a favorable safety profile with low rates of myelosuppression
- The efficacy and safety of radium-223 demonstrated in ALSYMPCA are based on a dosing regimen of 1 injection (50 kBq/kg) every 4 weeks for a total of 6 injections
- Radium-223 treatment beyond 6 injections has not been previously reported

### RATIONALE AND OBJECTIVE

- Given the acceptable safety profile, re-treatment with radium-223 may be well tolerated and provide added benefit to patients who received an initial course of 6 radium-223 injections
- Here we report the first safety and efficacy findings of radium-223 re-treatment from an international, prospective, open-label phase 1/2 trial in patients with bone-metastatic CRPC (NCT01934790)

### METHODS

- Study schema is presented in **Figure 1**

**Figure 1. Radium-223 Re-treatment Study Schema**


#### Eligibility

- Eligible adult patients had metastatic CRPC and ≥ 2 bone metastases and completed 6 initial radium-223 injections with
  - No progression in bone during the first course of treatment
  - Radiographic or clinical progression after initial treatment
  - Adequate hematologic laboratory values
  - Eastern Cooperative Oncology Group (ECOG) performance status 0-2
  - No visceral metastases ≥ 1 cm in diameter, or lymphadenopathy with nodes ≥ 6 cm and/or requiring local or systemic therapy
  - No prior systemic or hemibody external radiotherapy
  - No treatment with chemotherapy after initial course of radium-223
- No concomitant cytotoxic agents were permitted
- Other agents were permitted at investigator's discretion (ie, luteinizing hormone–releasing hormone [LHRH] analogs, flutamide, bicalutamide, nilutamide, cyproterone acetate, estramustine, ketoconazole, corticosteroids, estrogen, abiraterone, and enzalutamide)

#### End Points

- Primary: safety
- Exploratory: included time to radiographic bone progression, time to alkaline phosphatase (ALP) progression, and radiographic progression-free survival (rPFS) based on MRI/CT and bone scans performed every 3 months

### RESULTS

#### Patients

**Table 1. Demographics and Baseline Characteristics (ITT Population)**

| | Re-treatment N = 44* | ALSYMPCA N = 614 |
|---|---|---|
| Age, median (range), y | 71 (52-91) | 71 (49-90) |
| ECOG PS, n (%)<br>0<br>1<br>≥ 2† | 14 (32)<br>27 (61)<br>3 (7) | 165 (27)<br>371 (61)<br>77 (13) |
| Extent of disease, bone metastases, n (%)<br><6<br>6-20<br>>20, not superscan<br>Superscan | 18 (41)<br>15 (34)<br>6 (14)<br>5 (11) | 100 (16)<br>262 (43)<br>195 (32)<br>54 (9) |
| Prior docetaxel, n (%) | 20 (45) | 352 (57) |
| Prior abiraterone, n (%) | 27 (61) | NA |
| Prior enzalutamide, n (%) | 13 (30) | NA |
| Prior bisphosphonates, n (%) | 5 (11) | 121 (20) |
| Prior denosumab, n (%) | 21 (48) | NA |
| Hemoglobin, median (range), g/dL | 12 (9-16) | 12 (9-16) |
| Albumin, median (range), g/L | 39 (32-44) | 40 (24-53) |
| PSA, median (range), µg/L | 68 (< 1-2349) | 146 (4-6026) |
| LDH, median (range), U/L | 203 (115-532) | 315 (76-2171) |
| tALP, median (range), U/L | 85 (29-705) | 211 (32-6451) |

*Re-treatment safety analysis set.
†In re-treatment study, 9 patients had ECOG PS = 2; in ALSYMPCA, 1 radium-223 patient had ECOG PS = 2.
ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent-to-treat; LDH = lactate dehydrogenase; NA = not available; PSA = prostate-specific antigen; tALP = total alkaline phosphatase.

- A total of 44 patients were re-treated with radium-223; demographics and baseline characteristics versus ALSYMPCA are presented in **Table 1**
- Among the 44 patients, 29 (66%) completed re-treatment with all 6 injections
- Median number of injections received was 6
- Median time from end of initial radium-223 treatment was 6 months
- All patients had ≥ 2 prior hormonal regimens
- 20 (45%) patients had ≥ 1 prior chemotherapy regimen
- 32 (73%) failed prior novel hormonal agents (eg, abiraterone or enzalutamide)
- In the re-treatment study, 7 (16%), 12 (27%), and 4 (9%) patients had concurrent denosumab, abiraterone, and enzalutamide, respectively

#### Safety

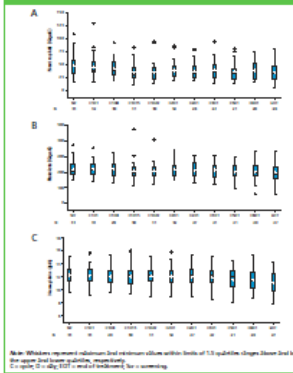
**Table 2. Treatment-Emergent Adverse Events (Safety Population)***

| | Re-treatment N = 44 | | ALSYMPCA N = 600 | |
|---|---|---|---|---|
| | All Grades | Grades 3 or 4† | All Grades | Grades 3 or 4 |
| Patients with ≥ 1 TEAE, n (%)‡ | 41 (93) | 21 (48) | 558 (93) | 339 (57) |
| Hematologic TEAEs, n (%) | | | | |
| Anemia | 6 (14) | 2 (5) | 187 (31) | 77 (13) |
| Thrombocytopenia | 1 (2) | 1 (2) | 69 (12) | 38 (6) |
| Leukopenia | 1 (2) | 0 | 25 (4) | 8 (1) |
| Neutropenia | 0 | 0 | 30 (5) | 13 (2) |
| Nonhematologic TEAEs in > 10% of patients in re-treatment study, n (%) | | | | |
| Fatigue | 12 (27) | 0 | 154 (26) | 24 (4) |
| Nausea | 11 (25) | 1 (2) | 213 (36) | 10 (2) |
| Diarrhea | 9 (21) | 0 | 151 (25) | 9 (2) |
| Decreased appetite | 8 (18) | 0 | 35 (6) | 2 (< 1) |
| Arthralgia | 6 (14) | 0 | 27 (5) | 3 (1) |
| Hypertension | 6 (14) | 5 (11) | 13 (2) | 3 (1) |
| Back pain | 5 (11) | 0 | 9 (2) | 3 (1) |
| Fall | 5 (11) | 0 | 6 (1) | 1 (< 1) |
| Vomiting | 5 (11) | 0 | 111 (19) | 10 (2) |

*Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (re-treatment), CTCAE v3.0 (ALSYMPCA).
†In re-treatment study, TEAEs presented, none were grade 5.
‡Recorded during treatment (end up to 30 days [re-treatment] or 12 weeks [ALSYMPCA] from 1st injection).
TEAEs = treatment-emergent adverse events.

- In this small study, no marked alterations in treatment-emergent adverse event (TEAE) incidence versus ALSYMPCA were observed (**Table 2**)
- Only 2 re-treatment patients had grade 3 hematologic TEAEs
- No grade 4 or 5 hematologic TEAEs were reported
- 2 patients reported serious ocular TEAEs (uveitis and glaucoma), both of whom had prior history of these ocular events, diabetic retinopathy, and other risk factors
- 5 patients reported nonserious ocular TEAEs (cataract, worsening of cataract, iritis with blurred vision, uveitis, glaucoma, and photopsia)
- All ocular TEAEs and serious TEAEs, with the exception of 1 nonserious grade 1 photopsia, were considered unrelated to radium-223 treatment

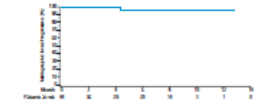
**Figure 2. Neutrophil (A), Platelet (B), and Hemoglobin (C) Values Over Time (Safety Population)**




- Neutrophil, platelet, and hemoglobin values were relatively unchanged over time (**Figure 2**)

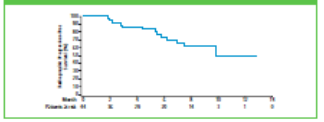
#### Exploratory Efficacy

**Figure 3. Kaplan-Meier Analysis of Time to Radiographic Bone Progression**



- Median time to radiographic bone progression was not reached (**Figure 3**)
- Only 1 patient had confirmed radiographic bone progression

**Figure 4. Kaplan-Meier Analysis of Time to Radiographic Progression-Free Survival**



- Median rPFS was 9.9 months (**Figure 4**)
- Among the 13 patients with rPFS events,
  - 8 had soft tissue tumor progression (4 lymph node only, 4 visceral metastases)
  - 2 had radiographic progression from disposition but not documented in radiographic tumor assessment
  - 2 died
  - 1 had confirmed radiographic bone progression
- Median time to total ALP progression was not reached

### CONCLUSIONS

- Radiographic bone progression with radium-223 re-treatment was rare, with the majority of disease progression occurring in soft tissue in this highly selected population
- Radium-223 re-treatment was well tolerated, with minimal hematologic toxicity, and provided continued control of disease progression in bone
- An ongoing study will address expanded radium-223 dosing and duration of treatment (NCT02023697)

### REFERENCES

1. Xofigo (radium Ra 223 dichloride) injection, for intravenous use [package insert]. Wayne, NJ: Bayer Healthcare Pharmaceuticals Inc; May 2013.
2. Parker et al. *N Engl J Med*. 2013;369:213-223.

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For questions or information regarding this poster, please contact Dr Oliver Sartor at osartor@tulane.edu.

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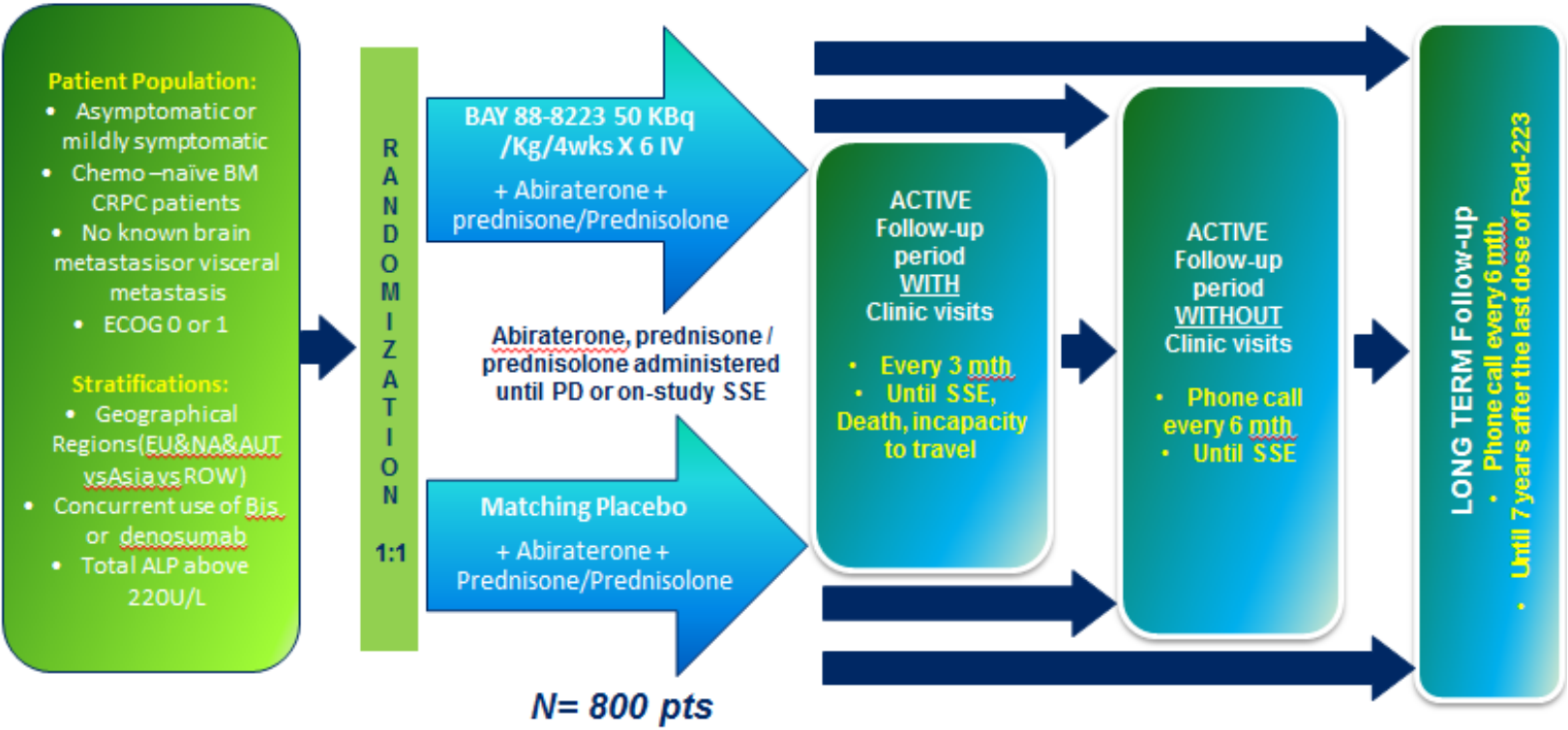
# Studio di fase III ERA-223

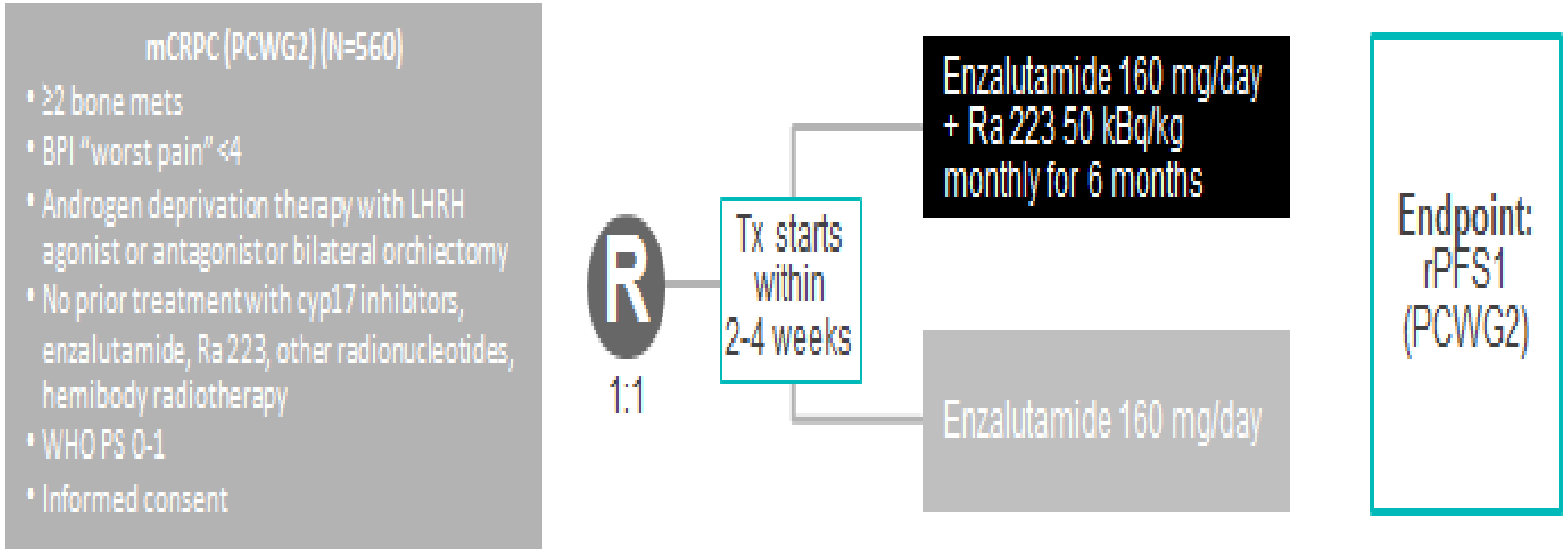
- Phase III; randomized, double blind, placebo-controlled
- Approximately 120 sites cross regions




- Chiuso all' arruolamento il 5 settembre 2016
- Paz. Randomizzati: 806

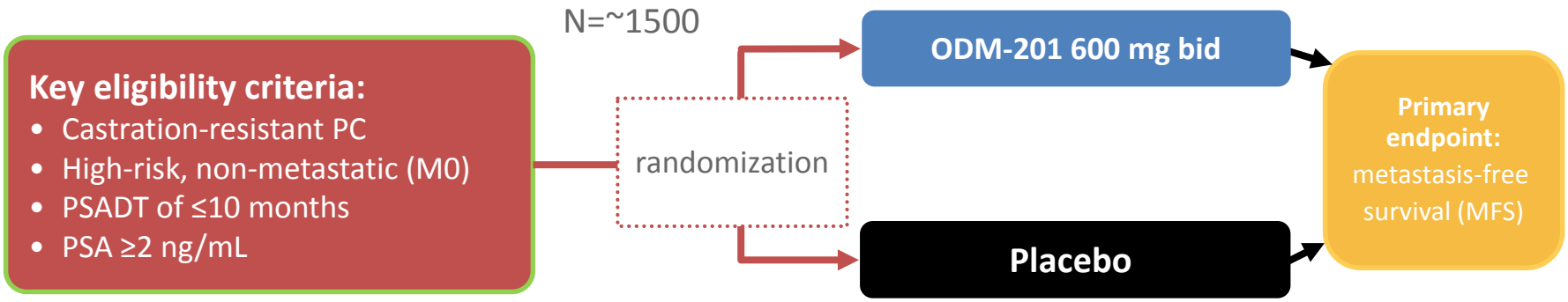
**Primary Endpoint:** SSE-FS
**Secondary Endpoints**: OS; Time to opiate use for cancer pain;Time to pain progression; HRQoL ; rPFS; Safety

# Studio randomizzato di fase III di Ra223 in combinazione con Enzalutamide vs Enzalutamide monoterapia (EORTC)




Previsti 560 pazienti; aperto all'arruolamento

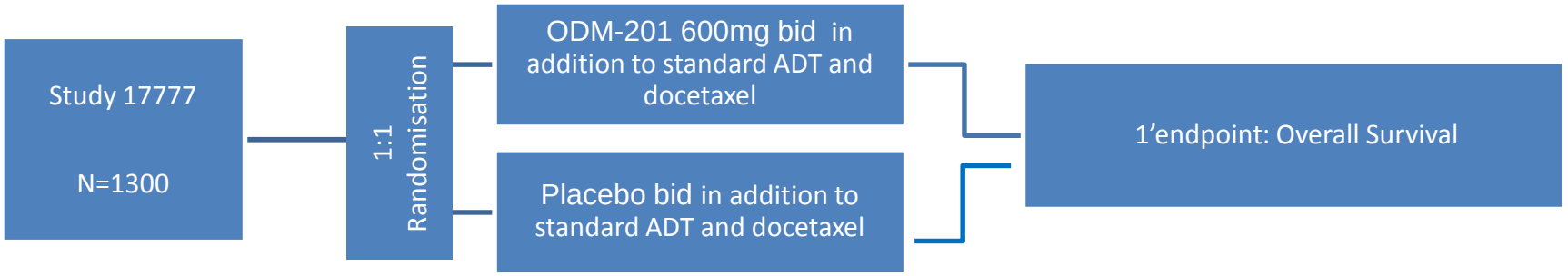
# ODM-201 ARAMIS Phase III Design




- FPFV Sept 2014
- Global study being conducted in about 400 centers in North and South Americas, Europe, Africa, and Middle East and Asia Pacific regions
- Timeline: primary study completion Q1 2018
- Secondary objectives include: OS, time to first symptomatic skeletal event, time to initiation of first cytotoxic chemotherapy for prostate cancer, time to pain progression, safety, and tolerability

**OS**, overall survival; **PC**, prostate cancer; **PSADT**, PSA doubling time.
Clinicaltrials.gov. NCT02200614. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02200614. Accessed August 2015.

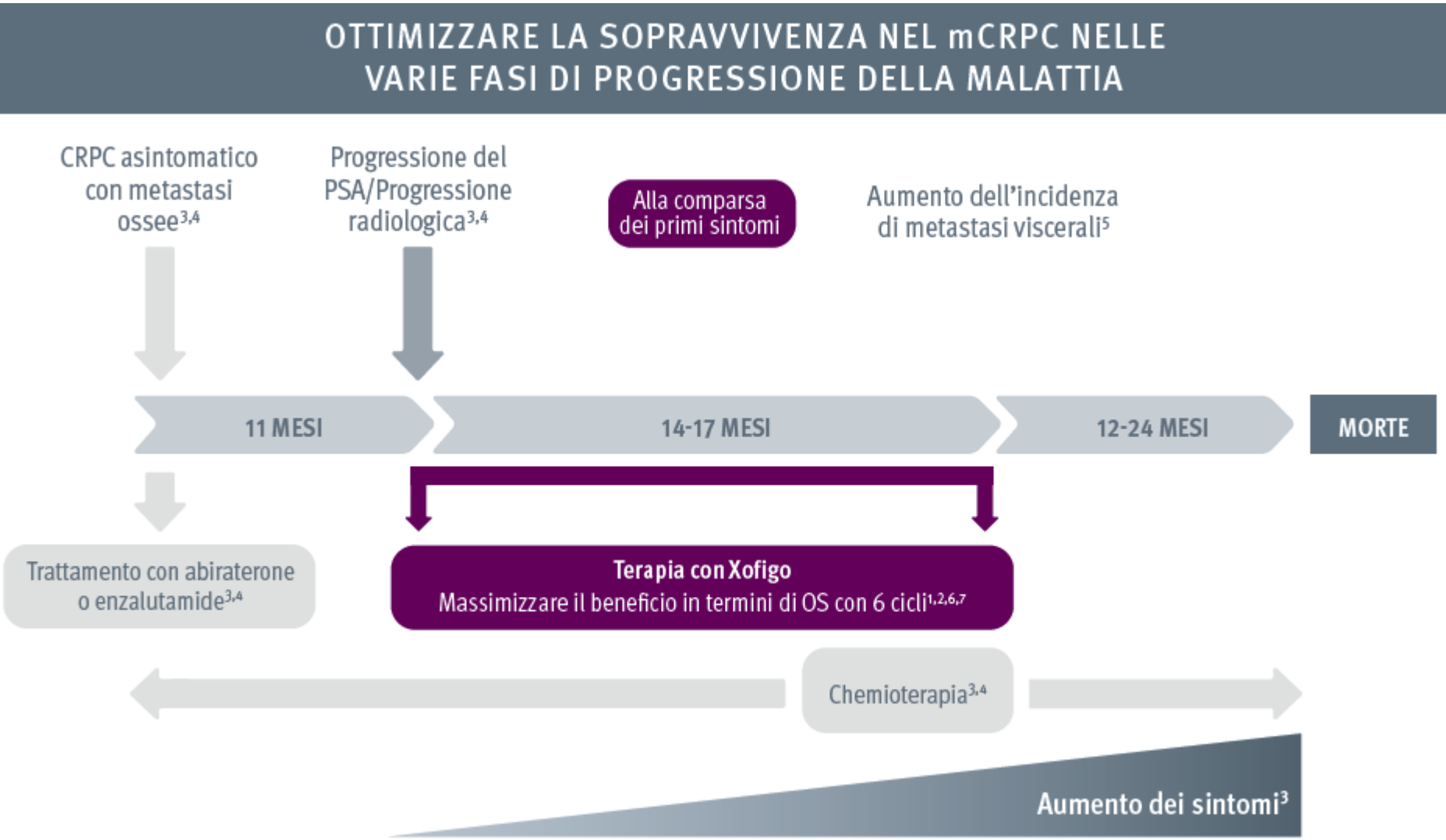
# **ARASENS**: A randomized, double-blind, placebo-controlled Phase III study of ODM-201 versus placebo in addition to standard androgen deprivation therapy and docetaxel in patients with metastatic hormone sensitive prostate cancer




**Key Eligibility Criteria:**

- Metastatic prostate cancer
- ADT started < 12 weeks before randomization (but no longer)
- Candidates for ADT and docetaxel
- ECOG 0-1

# Radio223: Take home message



# La targeted Alpha Therapy

| Terapia antiandrogeniche | **Targeted Alpha Therapy** | Chemioterapia | Terapia di supporto |
|---|---|---|---|
| ADT<br>Abiraterone<br>Enzalutamide | **Radium-223 dichloride** | Docetaxel<br>Cabazitaxel | Strontium-89<br>Samarium-153<br>Rhenium-186<br>Acido Zoledronico<br>Denosumab<br>Steroidi |

*Linee Guida AIOM 2016*

# Le domande che ci siamo fatti…

- ✓ **Paziente candidabile: anticipare il trattamento in accordo al label approvato, alle caratteristiche della malattia e alle aspettative del paziente: maggior efficacia e miglior safety**

- ✓ **Esperienza:**
  - **- TMD come strumento di condivisione e ottimizzazione**
  - **-importanza delle reti hub&spoke**

- ✓ **La malattia ossea ha un ruolo prognostico importante**

- ✓ **Gli AE sono generalmente lievi e ben gestibili**

- ✓ **Il farmaco è efficace e migliora la QoL del paziente**