

**Meta-analysis Of bone targeting RadioPHarmacEutical therapy
in patients with bone metastasis from Prostate cancer**

MORpheP

Initiated by the Institut de Cancérologie Gustave Roussy,
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Protocol

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CONTENTS

1. INTRODUCTION AND BACKGROUND	4
2. DESIGN	5
3. OBJECTIVES	5
4. TRIALS SELECTION CRITERIA	6
5. TRIAL SEARCH	6
6. DESCRIPTION OF TRIALS INCLUDED	8
7. ENDPOINTS AND COVARIATES	8
1/ Primary endpoint	8
2/ Secondary endpoints	8
3/ Prognostic factors	9
8. DATA COLLECTION AND QUALITY CONTROL	9
9. STATISTICAL ANALYSIS PLAN	10
10. PROJECT ADMINISTRATION	12
1/Working parties in the meta-analysis	12
2/Practical considerations	13
3/Contacting Trialists	13
11. PUBLICATION POLICY	13
REFERENCES	15
APPENDIX A: SEARCH STRATEGY FROM PUBMED	18
APPENDIX B: DESCRIPTION OF THE ELIGIBLE TRIALS	19
APPENDIX C: HOW TO SEND DATA TO THE SECRETARIAT	22

1. INTRODUCTION AND BACKGROUND

Prostate cancer is currently the first cancer in incidence and the second leading cause of cancer death in men in most Western countries. Although prostate cancer is initially sensitive to androgen deprivation, most deaths result from progression to castration-resistant status, with metastases spread usually involving the bones. In this setting, chemotherapy has demonstrated an improvement in the quality of life (1, 2), progression-free survival (2), and overall survival (3, 4). For a long time, the only drug with a survival advantage in this setting was docetaxel, but it has recently been joined by new products: abiraterone (5), cabazitaxel (6), the prostate cancer vaccine sipuleucel-T (7) and enzalutamid (7bis). However, the overall survival benefit is limited, with median survival being in the 18 months range in large phase III randomized trials.

Because of the important role of bone involvement in the progression of the disease, bone-targeted therapy with radiopharmaceuticals is a logical approach for castration-resistant prostate cancer (CRPC). Radiopharmaceuticals are radioactive agents with a high affinity for reactive bone sites and which deliver radiation to bone metastases in a highly focal manner. Early studies used radiopharmaceuticals for painful bone metastasis. Strontium (Sr) 89 (8) and samarium (Sm) 153-EDTMP (9, 10), have been the most extensively examined radiopharmaceuticals in clinical trials. Some reports also indicate objective tumor responses (evaluated by reduced serum PSA) in 64% of patients with CRPC treated with repeat low dose Sm 153-EDTMP, as well as a reduction in the number and volume of bone lesions for around 26% of patients with different primary tumors, including CRPC, after repeat standard dose treatment (11). These observations suggest that radiopharmaceutical therapy not only controls pain but may also have anti-tumor effects. Bone targeting radiopharmaceuticals have mostly been developed for pain management in patients with bone metastasis from CRPC. Pain was evaluated in the major cases using the visual analog scale (VAS) and the analgesic intake (dose modifications and type). Randomized trials showed a favorable effect on pain (8, 9) although this result has not been confirmed in other trials (12, 13). However, the use of bone targeting radiopharmaceuticals has been associated with bone marrow toxicity, with higher toxicity being reported with Sr 89 than Sm 153-EDTMP. This toxicity profile leads to difficulties in elaborating recommendations regarding the right time to introduce radiopharmaceuticals in CRPC: physicians may be afraid to introduce them early in the course of the disease to prevent long term anemia and thrombopenia. This suggests, also, difficulties to use subsequent chemotherapy. Although, late treatment by radiopharmaceuticals may be associated with limited or lack in efficiency.

Until recently, there was a debate regarding the improvement of overall survival in CRPC with radiopharmaceutical treatment. A survival benefit has been suggested in many small randomized trials (12) but not in all (10). Newly, Parkers et al was successful to demonstrate a survival advantage for patient CRPC with exclusively bone metastasis treated with Radium-223 dichloride, an alpha emitter particles, in the ALSYMPCA phase III study versus placebo (14) with mild toxicity.

It was also hypothesized that patients with a chemo-sensitive CRPC may be those who are likely to benefit from the use of radiopharmaceutical therapy in term of overall survival. In a randomized trial that tested maintenance doxorubicin with or without Sr 89 in 72 patients with CRPC who responded to induction chemotherapy, a better overall survival rate was reported in the combination arm with a median of 27.7 versus 16.8 months (15). More recently the association of docetaxel, the most active chemotherapeutic agent in this setting, and Sm 153-EDTMP has been evaluated as consolidation therapy in patients with CRPC and

bone metastases. The results reported a 77% response rate, a median overall survival of 29 months as compared to the expected one of less than 18 months, and a favorable pattern of tolerance, with only mild hematologic toxicity (16).

After the latest survival benefit shows by Radium-223 (14) in the CRPC and the good toxicity profile, this project will focus on the effect of radiopharmaceutical therapy compared with other protocols (placebo, external radiation, chemotherapy) with higher statistical power to detect an effect than in a single study. It will also permit to compare the efficacy of different types of radiopharmaceuticals (alpha-emitted radiation vs. beta-emitted radiation) and different association schemes. The second aim is trying to answer the question whether the effect of alpha emitters in this setting is only due to their biological mechanisms or to differences in study design, and patient selection.

This meta-analysis will be based on individual patient data (17) and will use methodology similar to that used in the MECaP study (18), MACH-NC study (19), the Breast Cancer Overview (Early Breast cancer Trialists collaborative Group) (20), the Prophylactic Cranial Irradiation Overview (21), and the Non Small Cell Lung Cancer Overview (The Non-Small Cell Lung Cancer Collaborative Group) (22). A similar collaborative group comprising those involved in trials included in the project will be established and the meta-analysis will be conducted and reported on its behalf.

Both published and unpublished studies will be included in the meta-analysis since there is evidence that both investigators and journal editors are more likely to publish trials with positive results (23). Basic survival and prognostic information will be collected for all patients randomized in each study because this allows a more reliable and flexible approach, a more sensitive analysis and avoids the potential bias of post-randomization exclusion (17, 24). When individual data will not be available, effort will be done by the collaborative group to collect detailed summary data. Updated follow-up information will be sought which will enable us to report on long-term survival.

In summary, the constitution of this unique database aims to answer the question of survival benefit related to radiopharmaceuticals in patients with bone metastasis from CRPC. Elucidating this issue is ultimately very useful for clinical practice.

2. DESIGN



A systematic review and meta-analysis based on updated individual patient data will be carried out and completed with summary data if needed. This approach involves the central collection, validation and analysis of data from all patients from all relevant randomized trials. When individual data will not be available, the group in charge of the trial will assure the control according to a process defined by the collaborative group.

3. OBJECTIVES

Assessment of the role of radiopharmaceuticals in the treatment of CRPC by studying the following questions:

Main objective

Role of different radiopharmaceuticals on the overall survival (OS) of patients with bone metastasis from prostate cancer by studying and comparing two arms:

-  Arm with a radiopharmaceutical therapy
-  Arm without a radiopharmaceutical therapy

Secondary objectives

- Comparison of the pain effect between the two arms
- Comparison of hematological toxicity between the two arms

4. TRIALS SELECTION CRITERIA

All trials must satisfy the following criteria:

Trials must

- Included patients with only prostate cancer or included several types of cancer but stratified on the type of cancer, only patients with prostate cancer
- Including more than 50 patients with a prostate cancer with available survival data
- Compare radiopharmaceuticals versus placebo, external radiotherapy or chemotherapy,
- Be randomized in a way which precludes prior knowledge of treatment assignment,
- Have completed accrual from 1993 to June 2013.

Patients should

- Have histologically-proven prostate cancer and disease progression after castration (either surgical or chemical castration using a LHRH agonist),
- Have evidence of metastatic bone disease.

5. TRIAL SEARCH

There is good evidence that investigators and journals alike are more likely to publish trials with positive results. In order to avoid such publication bias, both published and unpublished trials will be included in the meta-analysis. To identify as many relevant trials as possible, systematic searches of a number of trial sources have been carried out using electronic database searching for the period 1993-June 2013 (PubMed, Cochrane library), hand and internet searching (review articles, meeting proceedings of ASCO, ECCO, ESMO, ESTRO, ASTRO, The European association of nuclear medicine, EAU, AUA) and two trials register: clinicaltrials.gov and Cochrane. Search will be updated.

Electronic Databases

-Data from all published and unpublished randomized trials making the above comparisons in cancer patients has been sought: search strategy from Pubmed is described in **Appendix A**.

Trials Registers

- <http://www.clinicaltrials.gov> : Type of Cancer: Prostate cancer; Type of Trial: Treatment; Drug: Radiopharmaceutical, radiopharmaceuticals, strontium, samarium, radium, rhenium
- Cochrane library

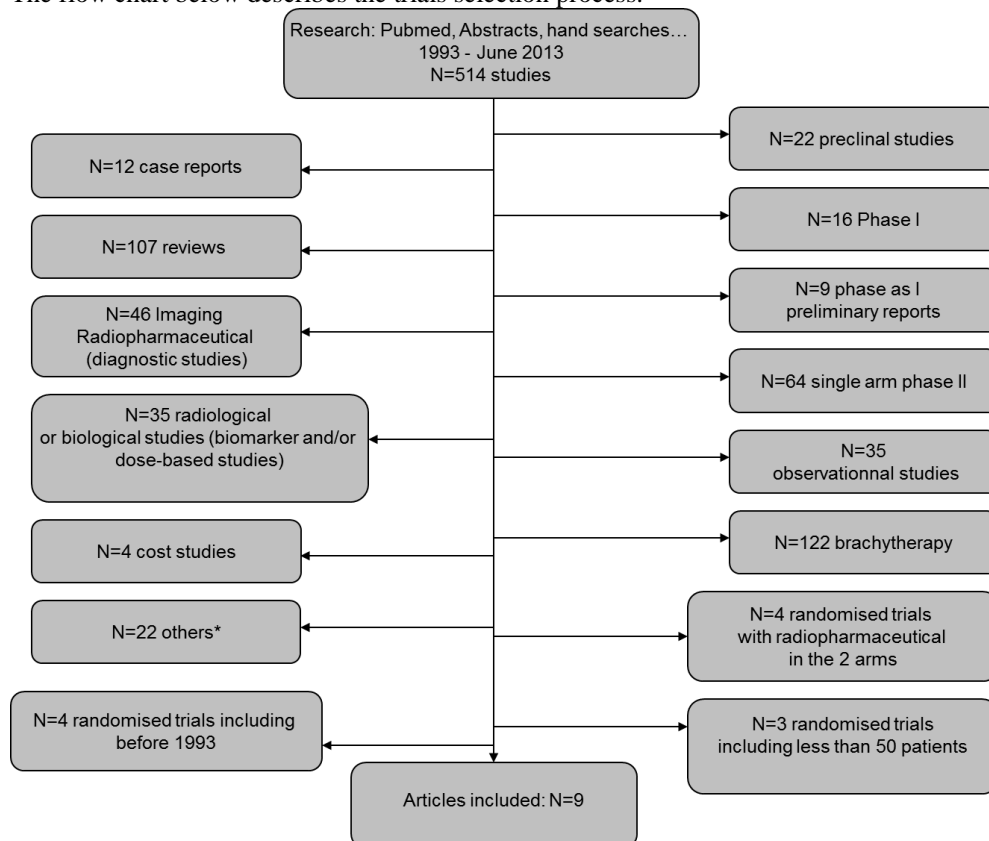
Hand Searches

Proceedings of ASCO, ECCO, ESMO, ESTRO, ASTRO, the European association of nuclear medicine, EAU, AUA: Abstract search for Radiopharmaceuticals, radiopharmaceuticals, samarium, strontium, radium, rhenium, in Title and randomized in Abstract.

Experts in the field

All participating trialists will be asked to review and supplement a provisional list of trials.

The flow chart below describes the trials selection process.



Note: two trials are both too small and too old.

*such as epidemiological studies, Therapeutics linked with radiopharmaceuticals, ...

6. DESCRIPTION OF TRIALS INCLUDED

The eligible trials are described in **Appendix B**. In total, nine trials including more than 2,000 (2422) patients, with two predominant trials (James et al and Nilsson et al) representing approximately 67% of total patients, studied the role of radiopharmaceuticals in patients with bone metastasis from prostate cancer (Table 1-A). Table 1-B summarizes the potential confounding factors in each trial.

We exclude 9 randomized trials because of several reasons: old accrual before 1993 (n=4), small studies including less than 50 patients (n=3) and trials randomizing radiopharmaceuticals in the two arms (n=4) (2 trials have old and small inclusion) (Cf. excluded Trials).

7. ENDPOINTS AND COVARIATES

1/ Primary endpoint

The main endpoint will be overall survival (OS) defined as the time from randomization until death or last follow-up evaluation.

2/ Secondary endpoints

- Anti-Pain effect: pain assessment required the use of validate instruments and involves a high degree of subjectivity. Data on pain intensity will be collected and depending on the available data, this endpoint will be analyzed or not. To make the evaluation of pain less subjective and homogenous between trials, the consumption of analgesic will also be used in considering it as a proxy: at a high pain corresponds a high consumption of analgesic. The type of analgesic will be defined from the WHO scale:

- 1: non opioid analgesic (paracetamol, aspirin, NSAID),
- 2: opioid for mild to moderate pain (codeine, tramadol, dextropropoxifen, ...)
- 3: opioid for moderate to severe pain (morphine, oxycodone, fentanyl,...)

Different expressions of the analgesic intake will be investigated according to the available data (type, dose, frequency). The time to pain progression will be also considered to evaluate the anti-pain effect of radiopharmaceuticals. The analysis of this criterion as secondary or exploratory will depend on the quality of data collection.

- Severe nausea, vomiting, hematological toxicity (including hemoglobin, white blood cells and platelets) (grade ≥ 3) and febrile neutropenia.

- Skeletal-related events (SREs). SREs are defined as pathologic bone fractures, spinal cord compressions (SCC), or bones metastasis for which external beam radiotherapy and surgical intervention is performed.

- Quality of life will not be analyzed since this data was not homogeneously measured or lacking in most trials.

- Progression-free survival (PFS) will not be analyzed because PFS does not qualify as a valid surrogate for survival (25) and its assessment is notoriously difficult in prostate cancer.

3/ Prognostic factors

The prognostic factors at baseline that will be considered, based on published data (25, 26) are:

- Age
- Performance status (2 classes: WHO 0/1 vs. 2+)
- Number of bone metastasis
- Serum PSA
- Alkaline phosphatase
- Hemoglobin level

8. DATA COLLECTION AND QUALITY CONTROL

For all eligible trials, basic survival and baseline characteristics will be sought for all patients randomized into each trial. When individual data will not be available, detailed summary data will be requested.

- Date of birth or age
- Performance status (baseline)
- Allocated treatment
- Date of randomization
- Date of last follow-up or death
- Survival status
- If death, cause of deaths
- Number of bone metastasis at baseline
- Serum PSA (baseline)
- Alkaline phosphatase (baseline)
- Hemoglobin level (at least at baseline)
- Pain at baseline and at every assessment (indicate the pain scale and dates of assessment) if possible
- Analgesic use (baseline), type of analgesic, the dose and the frequency of analgesic use per day, date of the first use of analgesic of type 3.
- Nausea, vomiting, hematological toxicity and febrile neutropenia (NCI grade recommended, specify if other grade used)
- Time to skeletal-related events (SREs). SRE component: pathologic bone fracture, spinal cord compression (SCC), external beam radiotherapy and surgical intervention
- Whether patients randomized in the non radiopharmaceutical group subsequently received radioisotopes at progression (Cross-over Yes/No) and date of cross-over

- Patients excluded from trial analysis, reasons for exclusion (if applicable)

Appendix C gives the suggested format and coding to be sent to the Secretariat.

All data will be checked for internal consistency and consistency with trial protocol and published report. Range checks will be performed and extreme values will be checked with the trialists. Each trial will be analyzed individually, and the resulting survival analyses and trial data will be sent to the trials for verification. These controls will be performed by the team in charge of the trial when individual data will be not directly available.

9. STATISTICAL ANALYSIS PLAN

Trial characteristics will be reported in tabular form, information will include patient numbers, period of recruitment, treatment details and median follow-up. Median follow-up will be computed using the reverse Kaplan-Meier method (27).

With a total of 1000 patients per group (920 events), a 0.05 level two-sided log-rank test for equality of survival curves will have 92% power to detect an hazard ratio HR=0.80 in favor of the radiopharmaceuticals group or a median survival difference from 12 to 15 months. It corresponds to show a difference in survival of 7% and 8% at 12 and 24 months, respectively.

The ultimate aim will be to obtain and analyze data from all randomized patients included in all of the relevant randomized trials. The principal analysis will be performed on the endpoint of overall survival. Additional analyses will be performed on anti-pain effect and toxicity.

All analyses will be carried out by intention to treat that is, patients will be analyzed according to the treatment allocated, **irrespective** of whether they received that treatment.

Survival analyses will be stratified by trial, and the log-rank expected number of deaths and variance will be used to calculate individual and overall pooled hazard ratios by the fixed-effect model (19, 28). Thus, the times to death for individual patients will be used within trials to calculate the hazard ratio, representing the overall risk of death for patients who were allocated to radiopharmaceutical therapy compared to those who were not. χ^2 heterogeneity tests will be used to test for gross statistical heterogeneity, the I^2 statistic (29) will be used as a measure of consistency. In presence of heterogeneity, random-effect model will be used. Stratified survival curves will be estimated for control and experimental groups using annual death rates and hazard ratio (20). They will be used to calculate absolute benefit at 1 and 2 years with their 95% confidence interval (20). As explanatory analysis, survival analyses adjusted on covariates will be done through multivariable Cox models. If results are similar with the non-adjusted analyses, only log-rank will be presented.

The analyses of anti-pain effect will be based on the analgesic intake due to heterogeneous measures of pain across the studies. According to the available data (type, dose, frequency of analgesic intake,...), different formulations of the consumption of analgesic will be explored among them: the time until the change of dose (time-to-event

analysis), the individual profile of analgesic intake over time (area under curve, linear mixed model for longitudinal data (30). In the last approach, the consumption of analgesic at time t will be computed as a weighted-sum of different type of analgesic.

Side effect analyses, for example severe toxicity (severe hematological toxicity (grade ≥ 3)) will also be stratified by trial and individual and overall pooled odds ratios will be calculated by a fixed-effect model. In case of heterogeneity, random-effect model will be used. As explanatory analysis, toxicity analysis adjusted on covariates will be done through multivariable logistic models. If results are similar with the non-adjusted analyses, only non-adjusted results will be presented.

The time to first skeletal-related events will be analyzed using survival methods. All p-values will be two-sided.

Subsets analyses: analyses by trial level characteristics

The main results will be presented globally and according to the following different groups:

(i) Type of radiation emitted from Radiopharmaceuticals

By type of radiation emitted from radiopharmaceutical: α emission (Ra223), β emission (Sm 153, Sr 89, Re 186).

(ii) Trial design and control arm

Selective trials when the radiopharmaceutical is the only variant between the trials arms: Radiopharmaceutical (RP) vs. placebo, Radiopharmaceutical (RP) + Chemotherapy (CT) (RP + CT) vs. Chemotherapy (CT), Radiopharmaceutical (RP) + External Radiotherapy (ERT) (RP + ERT) vs. External Radiotherapy (ERT), Radiopharmaceutical (RP) vs. External radiotherapy (ERT).

To evaluate the relevance of these subsets, the table summarizes the number of included patients by trial level characteristics.

Table: Number of included patients by trial level characteristics

Overall	2478
Type of radiation emitted	
<i>Alpha emission</i>	985 (2 trials)
<i>Beta emission</i>	1493 (7 trials)
Different types of comparison	
<i>RP vs. placebo</i>	1326 (5 trials)
<i>RP + CT vs. CT</i>	829 (2 trials)
<i>RP + ERT vs. ERT</i>	93 (1 trial)
<i>RP vs. ERT</i>	230 (1 trial)

Grouping trials comparing RP + CT vs. CT or RP + ERT vs. ERT will be investigated.

The OS as well as other endpoints will be compared between subsets defined by trial characteristics using the Q-Cochran heterogeneity test.

Sensitivity analyses

Analysis will be performed without the trial that included responder patients i.e. Tu's trial. Hazard ratios for overall survival will also be calculated excluding any trials that could be considered as outliers. Methods to study the impact of cross over will be decided before performing any analysis.

Subgroups analyses: analyses by patient level characteristics

Providing there are sufficient data available, we will investigate whether any observed treatment effect is consistent across well-defined patient subgroups. These analyses will be carried out on all trials and will be stratified by trial. If the treatment effect is not homogenous across trials within one subgroup, the subgroup analyses will be not performed.

If there are insufficient numbers of patients within any patient categories, some categories will be combined. Chi-squared tests for interaction or trend will be used to test whether there is any evidence that particular types of patients benefit more or less from radiopharmaceutical therapy. The method of pooling of within-trial covariate interaction (PWT) [31] will be used to test treatment-covariate interaction. It consists to compute the treatment-covariate interaction effect for each trial and combine them using the pooled inverse-variance method. Using this method, trials with no patient in some categories will be discarded of the inverse-variance pooled estimation. The assessment of heterogeneity is estimated using the Q statistic.

The subgroups are as follows:

- Age (3 classes)
- Performance status* (2 classes: WHO 0/1 vs. 2+) at baseline
- Serum PSA at baseline (3 classes)
- Hemoglobin level at baseline (3 classes)
- Alkaline phosphatase level at baseline (3 classes)

The 3 classes of the continuous variables will be defined by the thirtiles. When the number of patients in one category is considered insufficient, categories will be grouped into 2 classes.

*Performance status

WHO / ECOG	Karnofsky (%)
0	100, 90
1	80, 70
2, 3, 4	60-10

Before analyzing the data, the analysis plan will be finalized following discussion between the members of the Secretariat.

10. PROJECT ADMINISTRATION

1/Working parties in the meta-analysis

In order to realize the meta-analysis successfully, three groups with specific functions will be created: 1) the Secretariat 2) the Advisory Group 3) Meta-analysis Of bone targeting

RadioPHarmacEutical therapy in patients with bone metastasis from Prostate cancer (MORpheP-CG). The Secretariat is in charge of the coordination of the meta-analysis. It is responsible for completing the trial register and for inviting investigators to provide data available on patients. The Secretariat is also in charge of checking, processing and analyzing the data. Finally, the Secretariat is responsible for preparing reports, publications and works in very close collaboration with the Advisory Group.

The Advisory Group will include international experts in the field of oncology and nuclear medicine, involved in prostate cancer, and experts in meta-analysis. The list of its members will be given at the beginning of the protocol. The Advisory Group will support the Secretariat with medical and methodological expertise, help determine trials relevant to the overview, and promote contact between investigators and all the collaborators.

Meta-analysis Of bone targeting RadioPHarmacEutical therapy in patients with bone metastasis from Prostate cancer (MORpheP-CG) will include the investigators responsible for trials included in the meta-analysis. The members of the Secretariat and the Advisory Group will also be included in this group. Trialists will be responsible for providing the Secretariat with data on patients and for discussing the reports prepared by the Secretariat and the Advisory Group.

2/Practical considerations

The Secretariat, located in the Meta-Analysis Unit of the Biostatistics and Epidemiology Department at Gustave Roussy, will be responsible for liaising with trialists. The main database will be run by the Secretariat. All data, updating and correction should be sent there. When individual data is not available, the Secretariat send to the principal investigator of the trial, a table with the information needed and the standard operating process used to check the data. All supplied data will remain confidential and used exclusively for the meta-analysis. A meeting of all group members will be organized by the Secretariat to discuss the preliminary results.

3/Contacting Trialists

Trialists will be contacted, informed of the project, invited to collaborate and asked to supply data as outlined in the methods section, invited to participate to the investigator meeting and to review the manuscript(s).

11. PUBLICATION POLICY

The results of the meta-analyses will be published and presented in the name of “Meta-analysis Of bone targeting RadioPHarmacEutical therapy in patients with bone metastasis from Prostate cancer MORpheP”. Collaborative Group comprising trialists contributing data for analysis, the Secretariat and Advisory Group. Following publication in a peer reviewed journal, the meta-analyses will be submitted to the Cochrane Library to appear in the Cochrane Database of Systematic Reviews. One author from each trial will be co-author, and when appropriate other people who made a significant contribution to this study.

Suggested Timetable

- September 2013: Feasibility study, search for financial support, invitation of the investigators to participate to the study
- October 2014: Activation of the project
- March 2015-September 2015: data collection and data checking
- October 2015-December 2015: preliminary analysis and trialists meeting
- January 2016-June 2016: ASCO abstract submission/presentation of preliminary results (to be defined with the trialists)

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APPENDIX A: SEARCH STRATEGY FROM PUBMED

The search strategy used was:

- PUBMED: Prostate* [Title] OR "Prostatic carcinoma"[MAJR] AND "radioisotopes" , "radiopharmaceuticals", "Radiopharmaceutical" "samarium", "strontium", "radium", "rhenium" [MeSH and text word]) were combined with "bone" [MeSH and text word] , "pain"[MeSH and text word], metastasis [MeSH and text word]

Time from 1993 to June 2013

APPENDIX B : DESCRIPTION OF THE ELIGIBLE TRIALS

Table 1-A. Characteristics of the potentially eligible randomized trials

Study	Nb. of patients	Inclusion period	Arm without RP	Arm with RP	Description of RP	Trial design	Cross over
Strontium 89 groups							
Tu (1)	72*	1996-1999	Doxorubicine 8020 mg/m ² once a week x 6 weeks	Sr89:2.035 MBq/kg + doxorubicine	Single dose	Randomized phase II	No
Oosterhof (2)	203	NA (<2003)	Local ERT: usual radiotherapy regimen used at the study centre	Sr89: 150 MBq (4mCi)	Single dose	Phase III	No
Smeland (3)	64	1997-2000	Local ERT: 3 Gy/fraction in 10 fractions or 8 Gy in one fraction. +Placebo	Sr89:150 MBq at J1 of ERT + local ERT	Single dose	Phase III	No
James (4)	757	NA (≤ 2012)	2 groups: A: Docetaxel 75mg/m ² /3w+prednisolone 10mg od (ST**). B: ST+ zoledronic Acid 4 mg (Cycle 1-10)	2 groups C: ST+ Sr89 150 MBq D: ST+ Zoledronic Acid 4 mg +Sr89 150 MBq (Cycle 1-10)	Single dose day 28 cycle 6	Phase III	No
Samarium 153 groups							
Serafini (5)	78	1992-1994	Placebo	Sm153: 0.5 mCi/Kg Or Sm153: 1 mCi/Kg	Single dose	Phase III: After 4 weeks non responders who received placebo receive 1.0 mCi/kg of RP in open-label conditions with the same 16-week follow-up evaluation; patients who received either dose of RP	Yes

were withdrawn from the study if their treatment was unblinded

Sartor (6)	152	NA (<2004)	Placebo	Sm153: 1 mCi/Kg	Single dose	Phase III: After 4 weeks non responders who received placebo receive Sm153 in open label manner. Unblinded patient who received RP were withdrawn from the study	Yes
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Radium-223 groups

Nilsson (7)	64	2004-2005	Placebo	Ra223: 50 kBq/kg/4weeks	4 IV administrations	Randomized phase II	No
Parker (8)	921	2008-2011	Placebo	Ra223:50 kBq/kg/4weeks	6 IV administrations	Phase III	Yes

Other groups

Han (9)	111	1993-1999	Placebo	Re186: From 1295 to 2995 MBq (no more details given)	Single dose	Phase III	No
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RP: radiopharmaceutical; Ra: radium, Re: rhenium, Sr: Strontium, Sm: Samarium, NA: Not available done; *: responders or stable after induction chemotherapy (maintenance treatment); ** ST: standard treatment, trial with a 2x2 design.

Table 1-B. Distribution of the eligible trials according to the potential confounding variables

Study	Nb. of Patients	Type of RP	Type of radiation emitted from RP	CT in both arms	RT in both arms	Type of comparison	Cross-over
Tu (1)**	72**	Sr 89	β	Yes	No	RP+CT vs CT	No
Oosterhof (2)	203	Sr 89	β	No	No	RP vs ERT	No
Smeland (3)	64	Sr 89	β	No	Yes	RP+local ERT vs ERT	No
James (4)	757	Sr 89	β	Yes	No	CT vs CT+ RP	No
Serafini (5)	78	Sm153	combined β and γ with a maximum of β -emission	No	No	RP vs Placebo	Yes
Sartor (6)	152	Sm153	combined β and γ with a maximum of β -emission	No	No	RP vs Placebo	Yes
Nilsson (7)	64	Ra223	α	No	No	RP vs Placebo	No
Parker (8)	921	Ra233	α	No	No	RP vs Placebo	Yes
Han (9)	111	Re186	combined β and γ with a maximum of β -emission	No	No	RP vs Placebo	No

Ra: radium, Re: rhenium, Sr: Strontium, Sm: Samarium

RP: radiopharmaceutical; ERT: external radiotherapy; CT: chemotherapy; RT: radiotherapy,

** Responders or stable after induction chemotherapy;

β : beta emitted radiation from radiopharmaceutical; α : alpha emitted radiation from radiopharmaceutical; γ : gamma emitted radiation from radiopharmaceutical suitable for scintigraphy imaging

References of randomized trials eligible for the meta-analysis

- 1- Tu SM, Millikan RE, Mengistu B et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *The Lancet* 2001; 357: 336-41.
- 2- Oosterhof GO, Roberts JT, de Reijke TM et al. Strontium(89) chloride versus palliative local field radiotherapy in patients with hormonal escaped prostate cancer: a phase III study of the European Organisation for Research and Treatment of Cancer, Genitourinary Group. *Eur Urol.* 2003; 44:519-26.
- 3- Smeland S, Erikstein B, Aas M et al. Role of strontium-89 as adjuvant to palliative external beam radiotherapy is questionable: results of a double-blind randomized study. *Int. J. Rad Oncol Biol. Phys* 2003; 56: 1397–404.
- 4- James N.D, Pirrie S, Barton D, Brown JE, Billingham L, Collins SI, Daunton A, Birtle AJ, Chakraborti PR, Ford D, Hussain SA, Jones H, Pope A, Porfiri E, Russell JM, Stanley A, Staffurth J, McLaren D, Parker C, Wylie J. *J Clin Oncol* 31, 2013 (suppl; abstr LBA5000)
- 5- Serafini AN, Houston SJ, Resche I et al. Palliation of Pain Associated With Metastatic Bone Cancer Using Samarium-153 Lexidronam: A Double-Blind Placebo-Controlled Clinical Trial: *J Clin Oncol* 1998; 16: 1574-81.
- 6- Sartor O, Reid RH, Hoskin PJ et al. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology.* 2004; 63 :940-5.
- 7- Nilsson S, Franzen L, Parker C et al: Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study. *Lancet Oncol.* 2007; 8 :587-94.
- 8- Parker C, Nilsson S, Heinrich D, O’Sullivan J.M., Fosså S, Chodacki A, Wiechno P, Logue J, Seke M, Widmark A, Johannessen D.C, Hoskin P, Bottomley D, Coleman R, Vogelzang N, O’Bryan-Tear C.G, Garcia-Vargas J, Shan M., and Sartor O, for the ALSYMPCA Investigators. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. *N Engl J Med* 2013; 3:213-23.
- 9- Han SH, de Klerk JM, Tan S and al. The PLACORHEN study: a double-blind, placebo-controlled, randomized Radiopharmaceutical study with (186) Re-etidronate in hormone-resistant prostate cancer patients with painful bone metastases. Placebo Controlled Rhenium Study; *J Nucl Med.* 2002; 43:1150-6.

Excluded randomized trials

Trials randomizing radiopharmaceuticals in the two arms (n=4)

- Palmedo H, Manka-Waluch A, Albers P, Schmidt-Wolf IG, Reinhardt M, Ezziddin S, Joe A, Roedel R, Fimmers R, Knapp FF Jr, Guhlke S, Biersack HJ. Repeated bone-targeted therapy for hormone-refractory prostate carcinoma: randomized phase II trial with the new, high-energy radiopharmaceutical rhenium-188 hydroxyethylidenediphosphonate. *J Clin Oncol.* 2003; 21:2869-75
- Sciuto R, Festa A, Rea S, Pasqualoni R, Bergomi S, Petrilli G, Maini CL. Effects of low-dose cisplatin on 89Sr therapy for painful bone metastases from prostate cancer: a randomized clinical trial. *J Nucl Med.* 2002; 43:79-86
- Baczyk M, Czepczyński R, Milecki P, Pisarek M, Oleksa R, Sowiński J. 89Sr versus 153Sm-EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. *Nucl Med Commun.* 2007; 28:245-5
- Maxon III H.R., Schroder L.E., Hertzberg V.S., Thomas S.R., Englaro E.E., Samaratunga R., Smith H., Moulton J.S., Williams C.C., Ehrhardt G.J., Schneider H.J. Rhenium-186(Sn) HEDP for treatment of painful osseous metastases: results of a double-blind crossover comparison with placebo, *J. Nucl. Med.* 1991; 32:1877–81

Too old (accrual before 1993) and/or too small (n=5)

- Buchali K, Correns HJ, Schuerer M et al. Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *Eur J Nucl Med.* 1988; 14:349-51.
- Lewington VJ, McEwan AJ, Ackery DM et al. A prospective, randomised double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *Eur J Cancer.* 1991; 27:954-8.
- Porter AT, McEwan AJ. Strontium-89 as an adjuvant to external beam radiation improves pain relief and delays disease progression in advanced prostate cancer: results of a randomized controlled trial. *Semin Oncol.* 1993; 20 (Suppl 2):38-43.
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- Nilsson S, Strang P, Ginman C et al. Palliation of bone pain in prostate cancer using chemotherapy and strontium-89. A randomized phase II study. *J Pain Symptom Manage.* 2005; 29: 352-7.

APPENDIX C: HOW TO SEND DATA TO THE SECRETARIAT

FORMAT FOR THE DATA

Please provide data on all patients randomized. Data can be in almost any format (ASCII, Excel, Dbase, SAS...) but please indicate which format has been used. It would be helpful if you used the coding suggested, however you may code the data in the way that is most convenient for you. Please supply us with full details of the data coding system used.

If sending data via email (jean-pierre.pignon@gustaveroussy.fr, francoise.delassus@gustaveroussy.fr), please encrypt the data and let us know how it has been encrypted in a separate email, otherwise send us a compact disk at the administrative address noted at page 2.

Suggested coding and format for sending data by network mail or Compact disk

Variable	Format/Coding
Patient identifier	10 characters
Date of birth (or age at baseline)	dd/mm/yyyy, 99999999=Unknown for age: __ 2 digits, 99=unknown
Performance status at baseline	<ul style="list-style-type: none"> • For Karnofsky index: use 3 digits, • For WHO or ECOG index: use one digit (0 ou 1 ou 2 ou 3 ou 4)
Number of bone metastases (at baseline)	__ 2 digits, 99=missing
Serum PSA (ng/mL) at baseline (+ normal value)	__ . 3 digits, 999=missing
Serum PSA (ng/mL) normal value	__ . 3 digits, 999=missing
Hemoglobin (g/100mL) (at baseline)	__ . 3 digits, 999=missing
Alkaline Phosphatase (U/L) at baseline	__ . 3 digits, 999=missing
Alkaline Phosphatase (U/L) normal value	__ . 3 digits, 999=missing
Treatment allocated	1=No Radiopharmaceutical, (precise the type and details of treatment modalities) 2= Radiopharmaceutical
Type of Radiopharmaceutical	1=strontium, 2=samarium, 3=radium, 4=other
If other,	Specify
Date of randomization	dd/mm/yyyy, 99999999=Unknown
Date of last follow-up or death	dd/mm/yyyy, 99999999=Unknown
Survival status	0=Alive, 1=Dead
Cause of death	1= Cancer 2= Treatment-related 3= Other 4= Unknow
Pain at baseline (indicate the scale used)	1-3 digits
Dates of pain assessment	dd/mm/yyyy, 99999999=missing
Pain at assessment dates	1-3 digits
Type of analgesic use (at baseline)	1: non opioid analgesic (paracetamol, aspirin, NSAID) 2: opioid for mild to moderate pain (codeine, tramadol, dextropropoxifen, ...) 3: opioid for moderate to severe pain (morphine, oxycodone, fentanyl...)
Opioid analgesic (Type 3 only) used after baseline	0 = No opioid analgesic used 1 = Opioid analgesic used
Date of analgesic type 3 used (If analgesic type 3 used at baseline, this date is equal to randomization date)	dd/mm/yyyy, 99999999 = Unknown
Dose of analgesic	Precise the dose, the change of dose and the date of modification

Commentaire [A1]: B. Lacas et G. Le Teuff : Etendre à 4 chiffres avant la virgule vu les données de l'EORTC.

Commentaire [A2]: B. Lacas et G. Le Teuff : Etendre à 4 chiffres avant la virgule vu les données de l'EORTC.

Date of pathologic bone fracture	dd/mm/yyyy, 99999999=missing
Date of spinal cord compression (SCC)	dd/mm/yyyy, 99999999=missing
Date of external beam radiotherapy	dd/mm/yyyy, 99999999=missing
Date of surgical intervention	dd/mm/yyyy, 99999999=missing
Patient excluded from your analysis	0=No, 1=Yes
Reasons for exclusion	12 characters
Cross over to Radiopharmaceutical	0=No, 1=Yes, 9=missing
Date of cross over	dd/mm/yyyy, 999999=missing
Toxicity (maximum grade NCI recommended, specify if other grade used)	
Toxicity (maximum grade NCI recommended, specify if other grade used)	1 digit, 9=missing
Nausea/vomiting (NCI grade)	1 digit, 9=missing
Hematological toxicity: Hb (NCI grade)	1 digit, 9=missing
Hematological toxicity: WBC/neutropenia (NCI grade)	1 digit, 9=missing
Hematological toxicity: Platelets (NCI grade)	1 digit, 9=missing
Febrile neutropenia	yes=1, no=0, 9=missing