Ospedale
"Sacro Cuore - Don Calabria"

Incontri
di aggiornamento
del Dipartimento
Oncologico

Responsabile Scientifico:
Dott.ssa Stefania Gori

Tumori solidi e metastasi ossee: quali novità per il 2015?

SEDE
CENTRO FORMAZIONE
Ospedale "Sacro Cuore - Don Calabria"
Via Don Angelo Sempreboni, 5 - 37024 Negrar (Verona)

La Ricerca in Osteoncologia oggi

26/11/2015

Toni Ibrahim, BSc,MSc,MD,PhD
Centro di Osteoncologia e Tumori Rari
IRCCS – IRST, Meldola- Italy

A new emergency in oncology: Bone metastases in breast cancer patients. Ibrahim T, Mercatali L, Amadori D. Oncol Lett. 2013

Rapporto Cancro e Osso

EVOLUZIONE

Tumori primitivi → **le metastasi ossee e CTIBL**

RIVOLUZIONE:

- **Approccio multi e interdisciplinare: nascita dell'Osteoncologia**

- **Obiettivi: Prevenzione degli SRE e la storia naturale dei tumori (CTIBL)**

NATIONAL PROJECT: MULTIDISCIPLINARY APPROACH TO PATIENTS WITH BONE METASTASES

Prof Dino Amadori

2000 → **2015**

National training courses

2002 Bologna, Rome 2003 Naples, Bologna 2004 Naples, Forence

Publications: 3 books

2003 - 2011

National training and practical courses in Osteoncology

(Modena – Forlì- Roma- Verona- others)

→ **Course in Osteoncology**

2003 - 2005

II level University Masters in Osteoncology (Modena/Bologna/Forlì)

2009-2015

PhD in Osteoncology (Campus Roma)

→ **Masters/PhD in Osteoncology**

Establishment of Osteoncology Center

Establishment of Osteoncology field

Italian Society of Osteoncology — ISO — Società Italiana di Osteoncologia

→ **National Bone Metastases Data Base**

Centro di Osteoncologia

Oncologo

Infermiere dedicato

Radioterapistsa

Ricercatore di base

Palliativista

Data Manager

Paziente

Ortopedico

Anatomopatologo

Radiologo

Patologo clinico

Medico nucleare

Psicologo

Fisiatra

Obiettivi

Assistenza → Mono e Multidisciplinare

Ricerca → Preclinica, Traslazionale, Clinica

Formazione → Professionisti, Popolazione

Progettare insieme
le strategie di gruppo

Oncologo

Ricercatore di base

Infermiere

Centro di Osteoncologia

Data Manager/ Statistico

Farmacista

Studi epidemiologici in Osteoncologia

Studi epidemiologici retrospettivi in Osteoncologia conclusi

1- Santini D, Tampellini M, Vincenzi B, Ibrahim T, Ortega C, Virzi V, Silvestris N, Berardi R, Masini C, Calipari N, Ottaviani D, Catalano V, Badalamenti G, Giannicola R, Fabbri F, Venditti O, Fratto ME, Mazzara C, Latiano TP, Bertolini F, Petrelli F, Ottone A, Caroti C, Salvatore L, Falcone A, Giordani P, Addeo R, Aglietta M, Cascinu S, Barni S, Maiello E, Tonini G. Natural history of bone metastasis in **colorectal cancer**: final results of a large Italian bone metastases study. Ann Oncol. 2012

2- Silvestris N, Pantano F, Ibrahim T, Gamucci T, De Vita F, Di Palma T, Pedrazzoli P, Barni S, Bernardo A, Febbraro A, Satolli MA, Bertocchi P, Catalano V, Giommoni E, Comandone A, Maiello E, Riccardi F, Ferrara R, Trogu A, Berardi R, Leo S, Bertolini A, Angelini F, Cinieri S, Russo A, Pisconti S, Brunetti AE, Azzariti A, Santini D. Natural history of malignant bone disease in **gastric cancer**: Final result of a multicentric bone metastasis survey. PloS One 2013

3- D. Santini, G. Procopio, C. Porta, T. Ibrahim, S. Barni, C. Mazzara, A. Fontana, A. Berruti, R. Berardi, B. Vincenzi, C. Ortega, D. Ottaviani, G. Carteni, G. Lanzetta, V. Virzì, N. Silvestris, M. A. Satolli, E. Collovà, A. Russo, G. Badalamenti, S. L. Fedeli, F. M. Tanca, V. Adamo, E. Maiello, R. Sabbatini, A. Felici, G. Tonini, S. Bracarda. Natural History of Malignant Bone Disease in **Renal Cancer**: Final Results of an Italian Bone Metastasis Survey. Plos One 2013

4- Vincenzi B, Frezza AM, Schiavon G, Santini D, Dileo P, Silletta M, Delisi D, Bertoldo F, Badalamenti G, Baldi GG, Zovato S, Berardi R, Tucci M, Silvestris F, Dei Tos AP, Tirabosco R, Whelan JS, Tonini G. Bone metastases in **Soft Tissue sarcoma**: a survey of natural history, prognostic value and treatment options. Clin Sarcoma Res. 2013

5- Santini D, Pantano F, Riccardi F, Di Costanzo GG, Addeo R, Guida FM, Ceruso MS, Barni S, Bertocchi P, Marinelli S, Marchetti P, Russo A, Scartozzi M, Faloppi L, Santoni M, Cascinu S, Maiello E, Silvestris F, Tucci M, Ibrahim T, Masi G, Gnoni A, Comandone A, Fazio N, Conti A, Imarisio I, Pisconti S, Giommoni E, Cinieri S, Catalano V, Palmieri VO, Infante G, Aieta M, Trogu A, Gadaleta CD, Brunetti AE, Lorusso V, Silvestris N. Natural History of malignant bone disease in **hepatocellular carcinoma**: Final results of a multicenter bone metastasis survey.PLoS One. 2014

6- Daniele Santini, sandro barni, salvatore intagliata, alfredo falcone, francesco ferraù, Domenico Galetta, luca moscetti, nicla la verde, toni ibrahim, fausto petrelli, Enrico Vasile, laura ginocchi, davide ottaviani, Flavia Longo, cinzia ortega, Antonio Russo, giuseppe badalamenti, elena collovà, gaetano lanzetta, giovanni mansueto, vincenzo adamo, filippo de marinis, maria antonietta satolli, flavia cantile, andrea mancuso, francesca maria tanca, raffaele addeo, marco russano, Michelle Sterpi, Francesco Pantano, Bruno Vincenzi, and Giuseppe Tonini. NATURAL HISTORY OF **NON-SMALL-CELL LUNG CANCER** WITH BONE METASTASES. Scientific Reports in press.

Studi epidemiologici retrospettivi in Osteoncologia ongoing

A- Natural history of bone metastasis in **Head and Neck cancer**: a large Italian bone metastases study.

Coordinator: Alfredo Berruti

B- Natural history of bone metastasis in **Neuroendocrine Neoplasms**: a large Italian bone metastases study.

Coordinator: Nicola Fazio

Studio epidemiologico prospettico in Osteoncologia

Banca Dati Nazionale Metastasi Ossee

Banca Dati Nazionale Metastasi Ossee

- Obiettivi -

- Valutazione dell'impatto epidemiologico e clinico delle metastasi ossee
- Valutazione dell'impatto del trattamento
- Caratterizzazione biologica
- Studio dell'efficienza complessiva del percorso dei pazienti con metastasi ossee

- Inserimento dei dati -

- Utilizzo di un software on-line costruito "su misura" previo il rilascio di username e password;
- Garanzia di completezza, affidabilità e risultati certi ed incontrovertibili;
- Raggiungimento di un campione di pazienti omogeneo.

I dati di ciascun paziente verranno aggiornati dal centro con periodicità semestrale fino all'exitus del paziente stesso.

Contenuto della banca dati

A. *Dati demografici del paziente, nel rispetto dell'anonimato*: sesso, anno di nascita, residenza e stato in vita;

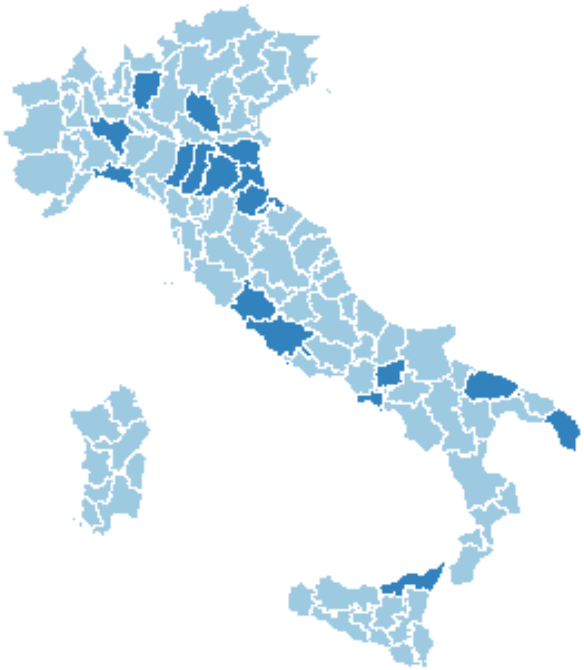
B. *Dati minimi clinico-epidemiologici e biologici sul tumore primitivo*: data di diagnosi, sede, morfologia, grading, stadio, recettori, terapia adiuvante e radioterapia locale;

C. *Dati clinici inerenti la prima ricaduta ossea*: data di diagnosi, sede, caratteristiche dei trattamenti a cui il paziente si è sottoposto;

D. *Dati clinici sulla storia naturale delle nuove metastasi ossee:* data di diagnosi, sede, caratteristiche trattamento chirurgico, farmacologico, interventistico, radioterapico e radiometabolico oltre a informazioni su data e tipo di eventuale SRE sviluppato.

I centri attualmente partecipanti

Centri aperti: IRST, Lugo, Rimini, Campus (Roma), Vito Fazzi (Lecce), Bari, Carpi, Pascale (Napoli), Taormina, Imola, Negrar (Verona) , Piacenza, Cuneo, Cardarelli (Napoli), Reggio E., Treviglio, Benevento, San Matteo Pavia, Belcolle (Viterbo), Genova, Ferrara. (**21 centri**)



Sei centri in attesa di delibera autorizzativa locale.

Un centro in sottomissione al CE locale / in attesa di approvazione da parte del CE.

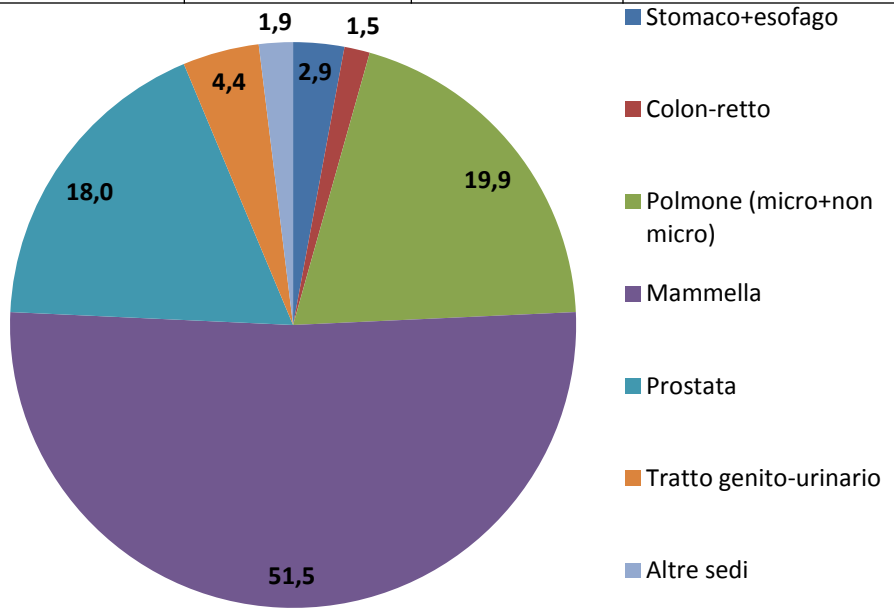
Tre centri in attesa di sottomissione al CE locale.

Centro coordinatore: Centro di Osteoncologia
IRCCS- IRST, Meldola (FC)
toni.ibrahim @irst.emr.it
flavia.foca@irst.emr.it

Alcuni dati

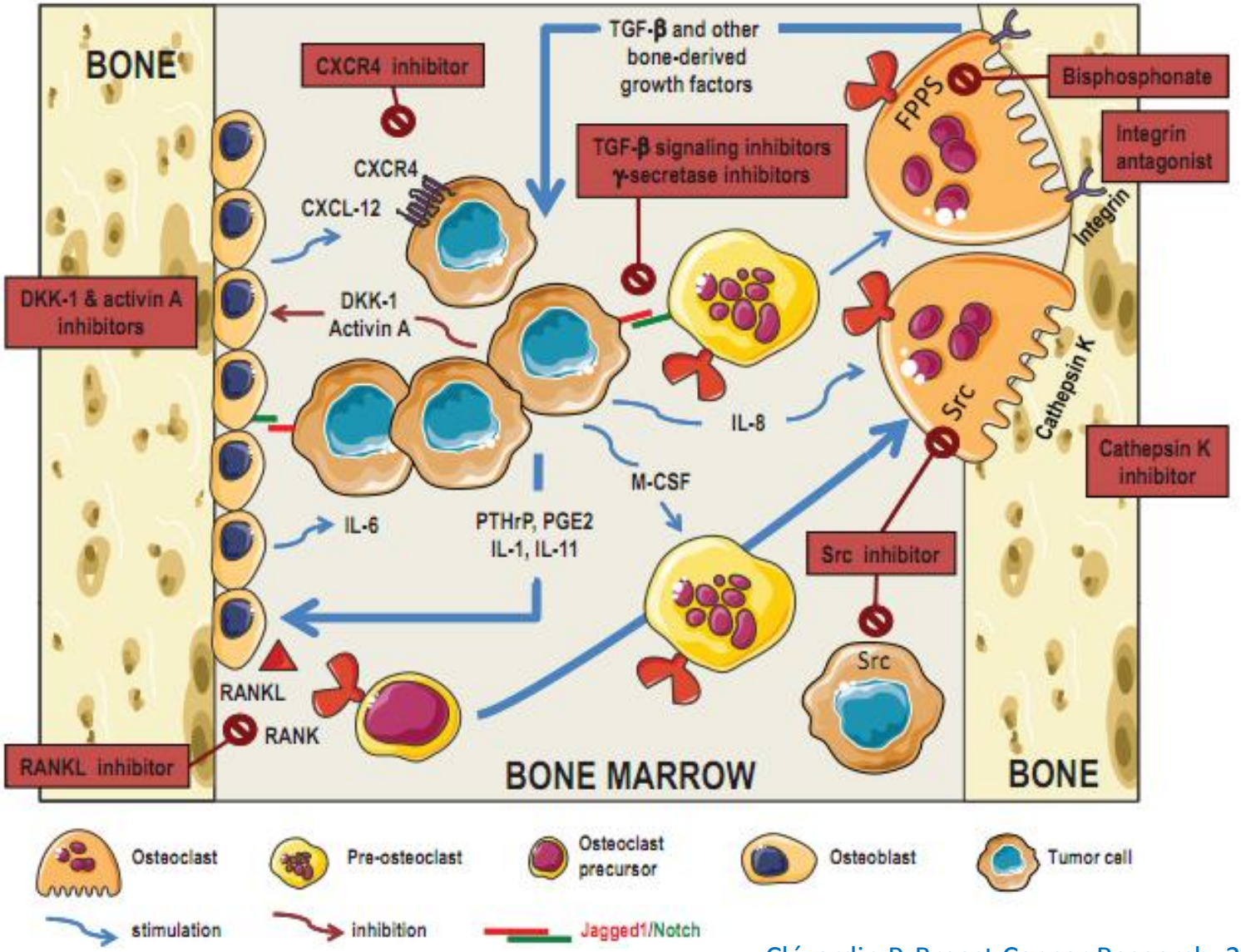
Centro	Data attivazione	Numero di record inseriti					
		Anagrafica	Tumore primitivo	Prima metastasi ossea	SRE su prima metastasi ossea	Aggiornamento meta ossea	SRE su aggiornamento meta ossea
TOTALE Casi inseriti	**-**	***247***	***206***	***139***	***22***	***97***	***8***
IRST	08/10/2013	**117**	**117**	**53**	10	**61**	**6**
Lugo	14/05/2014	**4**	**3**	**4**	0	**6**	0
Rimini	06/05/2014	**39**	**35**	**32**	2	**7**	**1**
Osp. Vito Fazzi Lecce	12/11/2014	**23**	**23**	**23**	**7**	**23**	**1**
Policlinico Bari	11/02/2015	**14**	**14**	**13**	**3**	0	0
Carpi	17/02/2014	**14**	**14**	**14**	0	0	0
Piacenza	16/06/2015	**36**	0	0	0	0	0

Sono presenti 104 maschi (42.1%) e 143 femmine (57.9). L'età mediana dei pazienti è 62 anni (25-75% percentile:54-71 anni). Il 47% dei pazienti afferisce all'IRST di Meldola.



Studi clinici in Osteoncologia

Bone Targeted Therapy

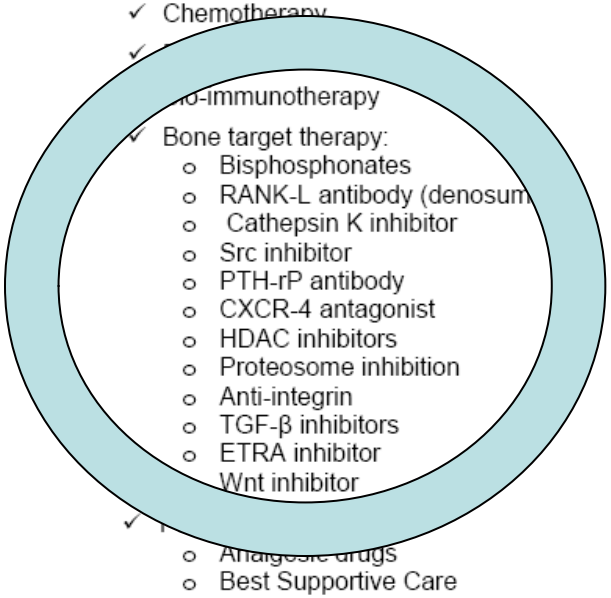


Clézardin P, Breast Cancer Research, 2011

Treatment of Bone Metastases

Treatment of Bone Metastases

Medical treatment



Radiotherapy

Radiometabolic treatment

Orthopedic surgery

Interventional radiology

Rehabilitation

RANK-L, receptor activator of nuclear factor-kb ligand; PTH-rP, parathyroid hormone-related peptide; CXCR-4, chemokine receptor type 4; HDAC, histone deacetylase;TGF-β, tumor growth factor β; ETRA, endothelin receptor A

Schedules

Medical treatment of bone metastases has become progressively complex and currently includes:

✓ well known antitumor agents

✓ **bone targeted molecules**

Ibrahim T, Tumori 2013

Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): a phase 3, open-label, randomised, non-inferiority trial.

Amadori D, Aglietta M, Alessi B, Gianni L, Ibrahim T, Farina G, Gaion F, Bertoldo F, Santini D, Rondena R, Bogani P, Ripamonti CI. Lancet Oncol. 2013

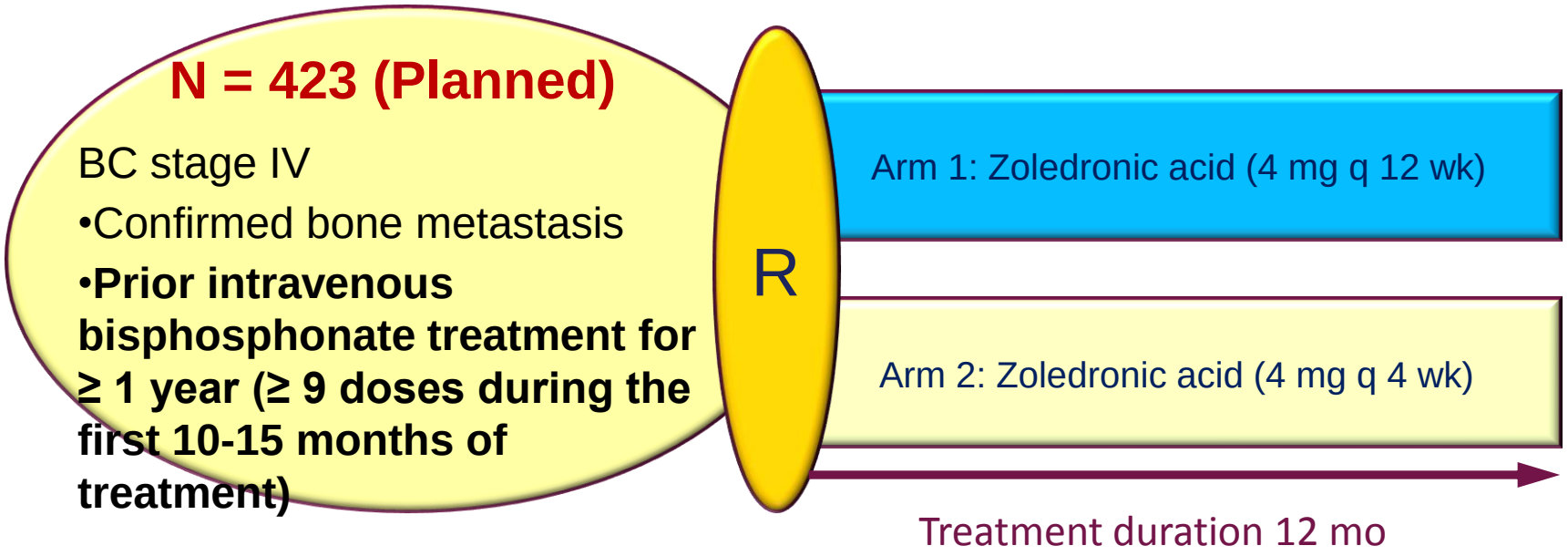
ZOOM: Summary

- ZOOM is the first trial to compare quarterly vs monthly ZOL in BC patients after ~1 y of standard ZOL therapy
- Primary endpoint of SMR was met: q 12 wk ZOL was non-inferior to q 4 wk ZOL
- Safety profiles of the 2 treatment schedules were similar
  - No meaningful differences in renal AEs or ONJ event rates
- Exploratory analyses of median NTX levels showed an increase from baseline in the q 12 wk arm, but almost no change in the q 4 wk arm

Abbreviations: AE, adverse event; BC, breast cancer; NTX, N-telopeptide of type I collagen; ONJ, osteonecrosis of the jaw; q, every; SMR, skeletal morbidity rate; ZOL, zoledronic acid.

OPTIMIZE-2: Study Design

- **Primary endpoint:** Proportion of patients with at least 1 SRE on study (non-inferiority)
- **Secondary endpoints:** Time to first SRE, bone pain on study, bone marker levels (NTX, BSAP)



Abbreviations: BC, breast cancer; BSAP, bone-specific alkaline phosphatase; NTX, N-telopeptide of type I collagen; q, every; R, randomization; SRE, skeletal-related event.

http://www.clinicaltrials.gov. Identifier NCT00320710.

CALGB 70604 (Alliance): A randomized phase III study of standard dosing vs. longer interval dosing of zoledronic acid in metastatic cancer

Andrew L. Himelstein, Rui Qin, Paul J. Novotny, Drew K. Seisler, James L. Khatcheressian, John D. Roberts, Stephen S. Grubbs, Tracey O'Connor, Douglas Weckstein, Charles L. Loprinzi, and Charles L. Shapiro

Helen F. Graham Cancer Center & Research Institute, Newark, DE; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; Virginia Cancer Inst, Richmond, VA; Yale Univ, New Haven, CT; Roswell Park Cancer Institute, Buffalo, NY; New Hampshire Onc-Hem PA, Hooksett, NH; Mayo Clinic, Rochester, MN; Mount Sinai School of Medicine, New York, NY

PRESENTED AT: ASCO Annual '15 Meeting

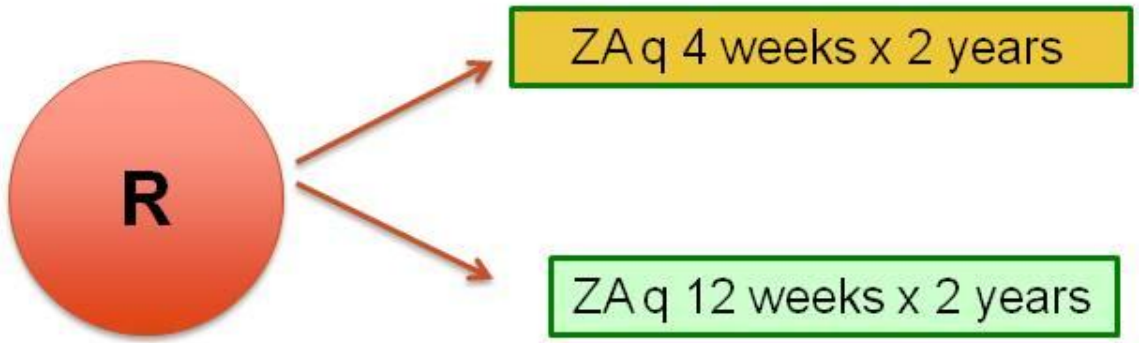
Presented By Andrew Himelstein at 2015 ASCO Annual Meeting

Prior Trials Looked at Dosing

- ZOOM breast cancer trial[1]
- OPTIMIZE-2 breast cancer trial[2]
- This trial is unique:
  - Includes breast cancer, prostate cancer, and multiple myeloma
  - Randomization starts with the initial dose

[1]Amadori, D, Agiletta, M, Alessi, B, et al. *Lancet Oncol.* 2013; 14:663-70
[2]Hortobagyi, GN, Lipton, A, Chew, HK, et al. *J Clin Oncol.* 2014; 32:5s (suppl; abstr LBA9500^)

Trial Schema



Stratifications:

1. Disease type
2. Baseline creatinine (≤ 1.4 or > 1.4 mg/dl)
3. Prior SRE
4. Prior oral bisphosphonate

Conclusions

- ZA administered every 12 weeks is **non-inferior** to ZA every 4 weeks
- No significant differences:
  - Disease site
  - Skeletal morbidity rates
  - Pain scores
  - Performance status
  - Osteonecrosis of the jaw, renal dysfunction

NSCLC (tutte le linee) **Studio AIFA ongoing – Prof Iacobelli, Chieti**

A prospective, multicenter, phase III, randomized, non-inferiority trial comparing zoledronic acid administered every 12 weeks vs every 4 weeks in Non Small Cell Lung Cancer (NSCLC) patients with metastatic bone disease (ZEN study)

Rationale:

Lung cancer is the leading cause of death from cancer worldwide and most of the patients will develop bone metastases with a significant negative impact on quality of life and survival. Zoledronic acid (ZOL) is well recognized as the main treatment for patients with bone metastases from solid tumors and multiple myeloma.

The goal of this study is to compare the efficacy and safety of ZOL administered at a longer dosing interval (12 weeks) versus the standard dosing interval (4 weeks) in patients with Non Small Cell Lung Cancer (NSCLC) with bone metastases.

Study design: Prospective, multicenter, phase III, randomized, open-label, non-inferiority trial. Subjects will be randomized in a 1:1 ratio to receive ZOL every 12 weeks or every 4 weeks.

NSCLC (tutte le linee) Studio AIFA ongoing– Prof Iacobelli, Chieti

Primary objective: OS

Secondary objectives: PFS, number of patients developing osteonecrosis of the jaw, number of patients developing renal dysfunction or hypocalcemia, QoL, bone pain assessment, estimate of health-resource costs.

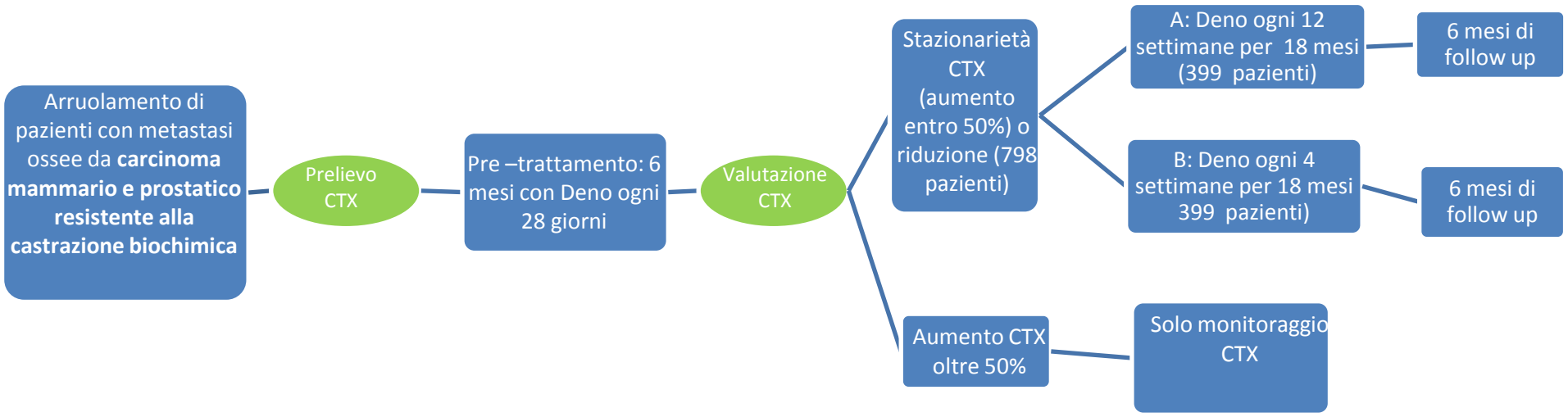
Study population:

- Histologically or cytologically confirmed diagnosis of NSCLC
- Male and female patients aged 18 years or older
- Life expectancy > 6 months
- At least one site of bone metastasis by radiologic imaging
- Adequate organ function
- Concurrent standard marketed antineoplastic therapies allowed
- Signed informed consent

DENO1: Multicentric randomized trial to evaluate the efficacy and safety of 12-weekly vs 4-weekly Denosumab in patients with bone metastases from breast or prostate cancer treated with 4-weekly Denosumab for 6 months (AIFA submitted 2012, II phase)

Study design: This is a randomized, open label, multicentric, non inferiority study to compare the reduced dose frequency (every 12 weeks[w]) of Deno with the continuation of the standard treatment (every 4 w) for 18 m in terms of prevention of SREs in pts with BMs from BPC who have already received 7 doses of Deno and obtained stable or a decrease in serum C-terminal telopeptide (CTX) values. A total of 798 patients will be enrolled (399 per arm). The accrual time is 36 m and treatment duration is 24 m.

Partecipating centers: Forty-one italian centers.



DENO1: Multicentric randomized trial to evaluate the efficacy and safety of 12-weekly vs 4-weekly Denosumab in patients with bone metastases from breast or prostate cancer treated with 4-weekly Denosumab for 6 months (AIFA submitted 2012, II phase)

Objectives of the study:

The primary efficacy endpoint of the study is the Skeletal Morbidity Rate (SMR) defined as the frequency of SREs occurring per year. All SREs occurring will be included in the evaluation: radiation therapy to bone, pathologic bone fracture, spinal cord compression, surgery to bone and hypercalcemia of malignancy.

Secondary objectives of this study are:

a- Time to first on-study SRE.
b- Proportion of patients who experience at least one SRE.
c- Proportion of patients experiencing a specific type of SRE.
d- Bone Response Rate (MD Anderson Criteria).
e- Time to bone progression.
f- Time to overall progression (bone and other sites).
g- Overall Survival.
h- Safety.
i- Bone pain score, assessed by the brief pain inventory (BPI) (short form).
j- Analgesic consumption, assessed by analgesic score.
k- Pharmacoeconomy.
l- Prognostic and predictive role of CTX, 25OHD (Vitamin D3) and PTH (Parathyroid hormone) and the identification of new circulating markers.

Treatment of Bone Metastases

Treatment of Bone Metastases

Medical treatment

- ✓ Chemotherapy
- ✓ [illegible]
- ✓ [illegible]-immunotherapy
- ✓ Bone target therapy:
  - Bisphosphonates
  - RANK-L antibody (denosum
  - Cathepsin K inhibitor
  - Src inhibitor
  - PTH-rP antibody
  - CXCR-4 antagonist
  - HDAC inhibitors
  - Proteosome inhibition
  - Anti-integrin
  - TGF-β inhibitors
  - ETRA inhibitor
  - Wnt inhibitor
- ✓ [illegible]
  - Analgesic drugs
  - Best Supportive Care

Radiotherapy

Radiometabolic treatment

Orthopedic surgery

Interventional radiology

Rehabilitation

RANK-L, receptor activator of nuclear factor-kb ligand; PTH-rP, parathyroid hormone-related peptide; CXCR-4, chemokine receptor type 4; HDAC, histone deacetylase;TGF-β, tumor growth factor β; ETRA, endothelin receptor A

Denosumab

Medical treatment of bone metastases has become progressively complex and currently includes:

✓ well known antitumor agents

✓ **bone targeted molecules**

Ibrahim T, Tumori 2013

EudraCT Number: 2013-001662-42	**Sponsor Protocol Number:**20120249	**Start Date*:** 2014-02-11
Sponsor Name: Amgen Inc		
Full Title: A Randomized, Double-blind, Multi-center Phase 2 Trial of Denosumab in Combination With Chemotherapy as First-line Treatment of Metastatic Non-small Cell Lung Cancer		

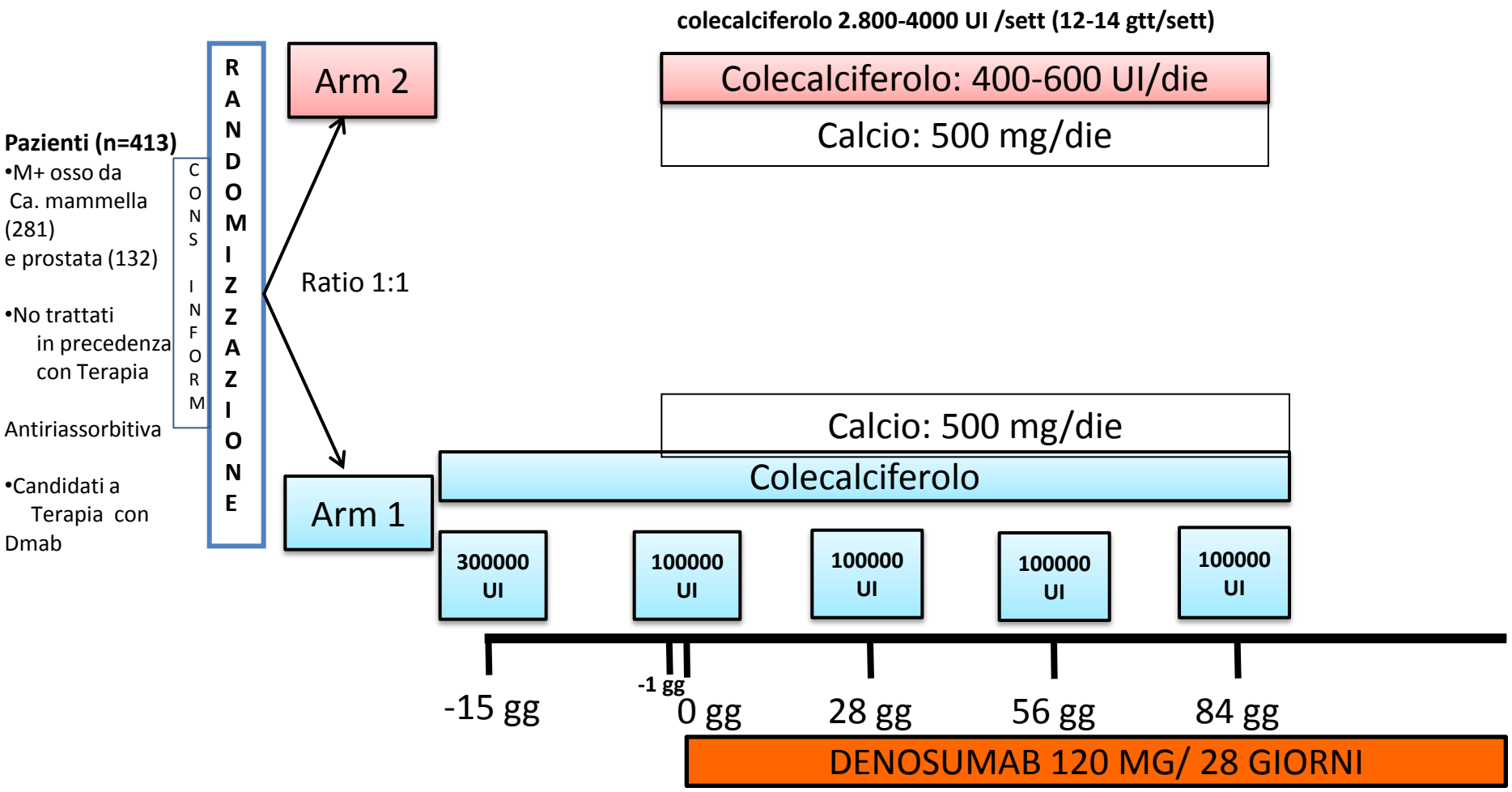
EudraCT Number: 2013-003156-21	**Sponsor Protocol Number:** ETOP_5-12/EORTC_08111	**Start Date*:** 2014-12-19
Sponsor Name:ETOP (European Thoracic Oncology Platform)		
Full Title: A randomised, open-label phase III trial evaluating the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC		

Valutazione dell'incidenza di ipocalcemia a breve termine con un nuovo schema di supplementazione con Vitamina D durante trattamento con Denosumab (120 mg) in pazienti con metastasi ossee da tumore mammario e prostatico (Studio Superman)

Studio di fase II, Randomizzato, Multicentrico, Controllato, No-profit

Coordinatori dello studio: Daniele Santini e Francesco Bertoldo
Data manager: Teresa Grassani

DISEGNO DELLO STUDIO



OBIETTIVI DELLO STUDIO

- **Obiettivo primario**:

  Confronto dell'incidenza di ipocalcemia di grado 2 o superiore tra i due bracci di trattamento durante i 3 mesi dello studio, stratificata per origine del tumore (prostata e mammella)

- **Obiettivi secondari**:

  -Confronto dell'incidenza globale (tutti i gradi di ipocalcemia) durante i 3 mesi dello studio, stratificata per origine del tumore,prostata e mammella

  -Confronto dell'incidenza d'ipocalcemia stratificata per grado di severità (grado 1,2,3,4,5)

  -Confronto dell'incidenza d'ipocalcemia sintomatica

  -Confronto del Tempo alla comparsa dell'evento ipocalcemico

  -Confronto della safety tra i due bracci trattamento

Treatment of Bone Metastases

Treatment of Bone Metastases	
Medical treatment	✓ Chemotherapy ✓ Endocrine therapy ✓ Bio-immunotherapy ✓ Bone target therapy: o Bisphosphonates o RANK-L antibody (denosumab) o Cathepsin K inhibitor o Src inhibitor o PTH-rP antibody o CXCR-4 antagonist o HDAC inhibitors o Proteosome inhibition o Anti-integrin o TGF-β inhibitors o ETRA inhibitor o Wnt inhibitor ✓ Palliative care: o Analgesic drugs o Best Supportive Care
Radiotherapy	
Radiometabolic treatment	
Orthopedic surgery	
Interventional radiology	
Rehabilitation	

RANK-L, receptor activator of nuclear factor-kb ligand; PTH-rP, parathyroid hormone-related peptide; CXCR-4, chemokine receptor type 4; HDAC, histone deacetylase;TGF-β, tumor growth factor β; ETRA, endothelin receptor A

Medical treatment of bone metastases has become progressively complex and currently includes:

✓ well known antitumor agents

✓ **bone targeted molecules**

Ibrahim T, Tumori 2013

PET-FLUORIDE **Studio IRST**

La PET/TC con ^{18}F-NaF nella valutazione delle metastasi ossee in pazienti affetti da tumore della prostata con sospetta recidiva biochimica.

Razionale: Una corretta gestione diagnostica e terapeutica dei pazienti con tumore della prostata è fondamentale sia in corso di stadiazione che durante il follow up. La ripresa di malattia infatti, a 10 anni dall'esordio, si verifica in circa il 20-30% dei pazienti trattati chirurgicamente e nel 50% dei casi radio trattati. La principale sede di metastasi secondaria da carcinoma della prostata è l'osso e risulta essere anche la principale causa di mortalità. E' quindi fondamentale fare diagnosi precoce di ripresa ossea di malattia in quanto le moderne terapie permettono una miglior sopravvivenza, sia in termini di tempo che di qualità della vita. La scintigrafia scheletrica con ^{99m}TC-difosfonati risulta essere il gold standard nella ricerca di lesioni ossee, tuttavia il recente sviluppo nella pratica clinica delle apparecchiature PET/CT ha fatto crescere l'interesse nei confronti di un altro tracciante osteotropo, non più γ emittente, ma β+ emittente. Il radiofarmaco in questione è il ^{18}F-sodio fluoruro (^{18}F-NaF), anch'esso capace di raggiungere la matrice ossea e fissarvisi in forma di cristalli di fluoro apatite. Recenti studi hanno evidenziato la superiorità in termini di accuratezza diagnostica della ^{18}F-NaF PET/CT rispetto alla scintigrafia ossea con ^{99m}TC-MDP con notevoli vantaggi in termini di sensibilità, specificità, tempi di esecuzione dell'esame, imaging tomografico e valutazione semiquantitativa, mediante calcolo del SUV.

PET-FLUORIDE **Studio IRST**

Disegno dello studio e obiettivi: studio prospettico
Obiettivo primario: valutare sensibilità, specificità e accuratezza della PET/ TC con ^{18}F-fluoruro di sodio rispetto alla scintigrafia scheletrica con ^{99m}TC-difosfonati ed alle altre metodiche di imaging convenzionale, nei pazienti affetti da carcinoma prostatico con ripresa biochimica di malattia.
Obiettivo secondario: secondo scopo dello studio sarà quello anche di valutare l'esistenza di una correlazione tra positività della PET/TC e valore del PSA sierico e ottenere un cut-off minimo di risoluzione.

Popolazione in studio

- **pregresso intervento di prostatectomia radicale per Ca prostatico o pregressa radioterapia con intento radicale;**

- **pazienti con incremento del PSA rispetto ad almeno tre valori stabili durante il follow up, anche per valori compresi tra 1 e 10 ng/ml;**

- **scintigrafia scheletrica con ^{99m}TC-difosfonati negativa e/o indeterminata;**

A three arm randomized open-label Phase II study of radium-223 dichloride 50 kBq/kg versus 80 kBq/kg versus 50kBq/kg in an extended dosing schedule in patients with castrate resistant prostate cancer metastatic to the bone.

Rationale: no rationale available at the moment. No data about phase I studies for treatment arm B and C; the treatment in arm A is the registered schedule and dosage.

Study design: International, multicenter, randomized, open-label phase II study. Subjects will be randomized to one of the 3 treatment arms in 1:1:1 fashion: radium-223 dichloride 50 kBq/kg iv every 28 days for up to 6 doses (Treatment Arm A) or radium-223 dichloride 80 kBq/kg iv every 28 days for up to 6 doses (Treatment Arm B) or radium-223 dichloride 50 kBq/kg iv every 28 days for up to 12 doses (Treatment Arm C).

Objectives:

The primary objective is to evaluate efficacy as measured by symptomatic skeletal event-free survival (SSE-FS) in the 3 arm

Symptomatic skeletal events (SSEs) are defined as:

o The use of external beam radiotherapy (EBRT) to relieve skeletal symptoms

o New symptomatic pathological bone fractures (vertebral and non-vertebral)

o Tumor-related orthopedic surgical intervention

o Spinal cord compression

The secondary objectives, are: safety and tolerability, OS, evaluate pain improvement, time to pain progression, time to first SSE

To evaluate time to radiological progression

To evaluate radiological progression-free survival (rPFS)

Study population:

- **Patients diagnosed with prostate adenocarcinoma**
- **Bone progression: two or more skeletal metastases (≥2 hot spots) on bone scintigraphy within 8 weeks of randomization**
- **ECOG PS 0-2**
- **No Visceral metastases**

Ritrattamento con alfa emittenti nella prostata Bayer

A re-treatment safety study of radium-223 dichloride in subjects with castration resistant prostate cancer with bone metastases who received an initial course of six doses of radium 223 dichloride 50 kBq/kg every four weeks.

Rationale: In the previous development studies, radium-223 dichloride at the dose of 50 kBq/kg has been administered for a maximum of 6 injections. Thus, the safety of re-treatment with radium-223 dichloride in subjects who had received an initial course of radium-223 dichloride has not yet been established. Since pain and its impact on quality of life are well established manifestations of bone metastases in prostate cancer, important objectives of prostate cancer treatment are the improvement of existing pain and the delay of clinical deterioration as a consequence of SREs that are associated with pain. The success of this strategy has been demonstrated using recently approved drugs such as abiraterone and enzalutamide. These drugs produced significant efficacy with respect to pain relief, delayed pain progression, and prevention of SREs in subjects with metastatic CRPC. Bone targeting beta emitting radiopharmaceuticals, such as strontium-89 and samarium-153, also palliate pain but with significant associated bone marrow toxicity. In phase I testing with this alfa emitter, there was evidence of pain relief at multiple dose levels.

Study design: **This is an international, multicenter, open label, safety study; phase I/II**

Ritrattamento con alfa emittenti nella prostata Bayer

Objectives:

The primary objective is to assess the safety of re-treatment with up to 6 doses of radium-223 dichloride 50 kBq/kg given every 4 weeks in subjects with castration-resistant prostate cancer (CRPC) with bone metastases who received an initial course of 6 doses of radium-223 dichloride 50 kBq/kg.

The exploratory objectives are: Radiological progression free survival, time to radiological bone progression, total alkaline phosphatase (ALP) response rate, time to total ALP progression, percentage change in total ALP, PSA response rate, Time to PSA progression, OS, pain response rate, time to pain progression, time to first skeletal related event (SRE), SRE-free survival.

Study population

- **patients diagnosed with metastatic CRPC/HRPC**
- **previous treatment with 6 injections of radium-223 dichloride 50 kBq/kg and no evidence of bone PD during the first course of treatment**
- **Progressive disease after radium 223 dichloride therapy**
- **no chemotherapy between the two treatments**
- **No Visceral metastases**

PEACE III **EORTC**

A Randomized multicenter phase III trial comparing enzalutamide vs. a combination of Ra223 and enzalutamide in asymptomatic or mildly symptomatic castration resistant prostate cancer patients metastatic to bone.

Rationale: The combination of enzalutamide and Ra223 ideally tackles two of the most important features of mCRPC, that are its ability to overexpress AR as a physiological adaptation to grow in a low testosterone environment and its high potential to grow in an environment where the bone remodeling is disrupted. The excellent safety profile of Ra223 and the non-overlapping mechanism of action make Ra223 potentially suitable for use in combination with enzalutamide.

Study design: This is a randomized phase III open label trial.

PEACE III **EORTC**

Primary endpoint: radiological PFS

Secondary endpoints: Overall survival; Prostate-cancer specific survival; First symptomatic skeletal event (SSE); Time and incidence of first skeletal progression ; Time to next systemic anti-neoplastic therapy; Second progression-free survival in sequential regimen; safety; Time to pain progression; Time to opiate use for cancer-related pain; QoL.

Study population

- histologically confirmed diagnosis of prostate adenocarcinoma
- Metastatic to bone with ≥ 2 bone metastases; no visceral mets
- Progressive CRPC according to Prostate Cancer Working Group 2 (PCWG2)
- Asymptomatic or mildly symptomatic
- Prior docetaxel is permitted under the following conditions: started within 2 months of Androgen Deprivation Treatment initiation, given for a maximum of 6 cycles and progression after 6 months of the last dose of docetaxel. Patients having received docetaxel for CRPC are excluded.

Title of Protocol: A phase II, randomized, double-blind, placebo-controlled trial of radium-223 dichloride vs placebo when administered to patients with metastatic Her 2 neg hormone receptor positive breast cancer with bone metastases treated with standard of care exemestane and everolimus

Location of Study: Global	**Phase:** II	**Route of Administration:** Intravenous	**Number of patients planned:** 323

Objectives:

The primary objective of this study is to compare, in subjects with Her 2 neg hormone receptor positive metastatic breast cancer with bone metastases treated with standard of care treatment exemestane and everolimus, the clinical benefit of radium-223 dichloride versus placebo, with the primary efficacy endpoint being:

- Symptomatic skeletal event free survival(SSE-FS)

The secondary objectives are to compare in subjects with Her 2 neg hormone receptor positive metastatic breast cancer with bone metastases treated with standard of care treatment with exemestane and everolimus, the clinical benefit of radium-223 dichloride versus placebo using the variables below:

- Overall survival (OS)
- Time to pain progression
- Time to cytotoxic chemotherapy
- Time to opioid use for cancer pain
- Radiological progression free survival (rPFS)
- Safety, acute and long term, including new primary malignancies and hematopoietic reserve for tolerability of subsequent chemotherapy

The study will also include the following exploratory endpoints:

- Time to first on-study symptomatic skeletal event
- Time to bALP progression
- bALP response
- Bone scan specific rPFS
- Resource utilization
- Biomarker assessments

An explorative objective is to evaluate the impact of baseline total body weight (TBW) and ideal body weight (IBW) on SSE-FS and adverse events

Treatment of Bone Metastases

Treatment of Bone Metastases	
Medical treatment	✓ Chemotherapy ✓ Endocrine therapy ✓ Bio-immunotherapy ✓ Bone target therapy: o Bisphosphonates o RANK-L antibody (denosumab) o Cathepsin K inhibitor o Src inhibitor o PTH-rP antibody o CXCR-4 antagonist o HDAC inhibitors o Proteosome inhibition o Anti-integrin o TGF-β inhibitors o ETRA inhibitor o Wnt inhibitor ✓ Palliative care: o Analgesic drugs o Best Supportive Care
Radiotherapy	
Radiometabolic treatment	
Orthopedic surgery	
Interventional radiology	
Rehabilitation	

RANK-L, receptor activator of nuclear factor-kb ligand; PTH-rP, parathyroid hormone-related peptide; CXCR-4, chemokine receptor type 4; HDAC, histone deacetylase;TGF-β, tumor growth factor β; ETRA, endothelin receptor A

Medical treatment of bone metastases has become progressively complex and currently includes:

✓ well known antitumor agents

✓ **bone targeted molecules**

Ibrahim T, Tumori 2013

Ultrasuoni focalizzati ad alta intensità guidati dalla Risonanza Magnetica 3 Tesla (MR-HIFU) nel trattamento del dolore da metastasi ossee da tumori solidi" – Studio IRST 198.01

IRST HIFU Team, Meldola 2015

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Obiettivo primario

Valutazione dell'efficacia degli ultrasuoni focalizzati ad alta intensità guidati dalla Risonanza Magnetica 3 Tesla (MR-HIFU) sull'intensità del dolore, inteso come dolore a riposo e dolore in movimento. Saranno considerate un successo del trattamento le risposte parziali (PR) e risposte complete (CR) a 30 giorni dal trattamento con MR-HIFU.

CR: pain score 0 nella scala NRS e no incremento analgesici

PR: riduzione di 2 o più nella scala NRS e no incremento analgesici; riduzione analgesici senza aumento dolore

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Obiettivi secondari

1. Evoluzione temporale della risposta al dolore durante il primo mese dopo il trattamento con MR-HIFU
2. Uso di analgesici (diminuzione nel consume di farmaci per il trattamento del dolore)
3. Sollievo dal dolore
4. Livello di soddisfazione del paziente
5. Qualità della vita
6. Controllo di malattia
7. Eventi collaterali
8. Valutazione dei marker circolanti (CTX, RANKL, mir-16, mir- 378 e altri marcatori) come predittori del sollievo dal dolore e controllo di malattia
9. Analisi costo efficacia confrontata con altri opzioni terapeutiche (inclusa la radioterapia)
10. Modifiche funzionali dell'imaging cerebrale.

PERCORSO SCREENING HIFU BONE

1° valutazione: **VISITA CDOM1:** selezione del paziente (lesione target + valutazione dolore) e firma consenso HIFU
Chiedere ad Oboldi per la 2° valutazione

↓

2° valutazione: **RMN MIRATA SU LETTINO HIFU:**
valutazione eleggibilità radiologica poi comunicare all'oncologo l'esito (Oboldi, Bazzocchi e Philips)

↓

3° valutazione:

- Esami ematici (studio HIFU bone/biologico)
- RX torace (se non ha fatto TC torace recente)
- PET/TC
- ECG + visita + Ecocardio
- **visita anestesiologica**

↓

Il paziente è eleggibile se ha l'OK delle 3 valutazioni.
Oncologo, radiologo e anestesista organizzano il trattamento HIFU

Bone Targeted Therapy

Advanced setting

↓

Adjuvant setting

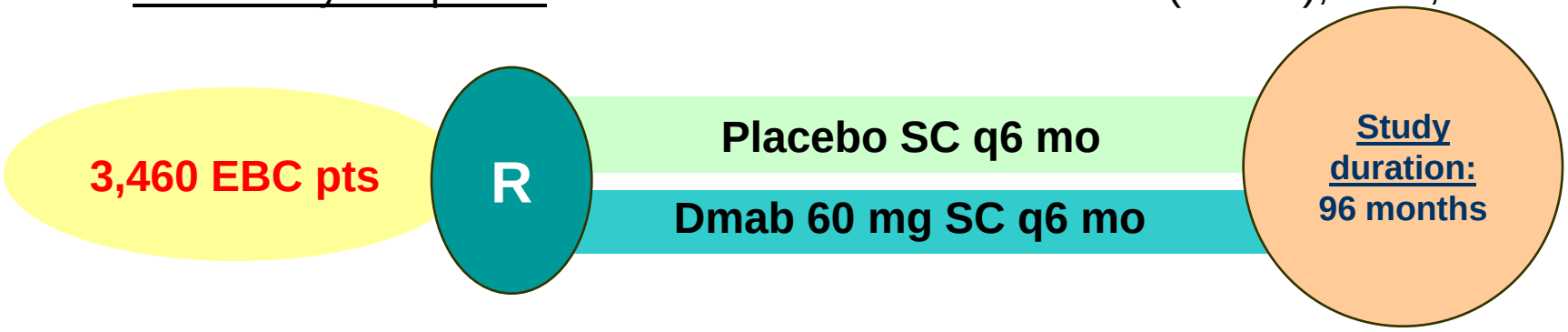
Hypogonadism
↑ RANKL/OPG

Predictive factors of Bone relapse (Bone tropism)

Denosumab in Early Adjuvant BC: ABCSG-18 & D-CARE Trials

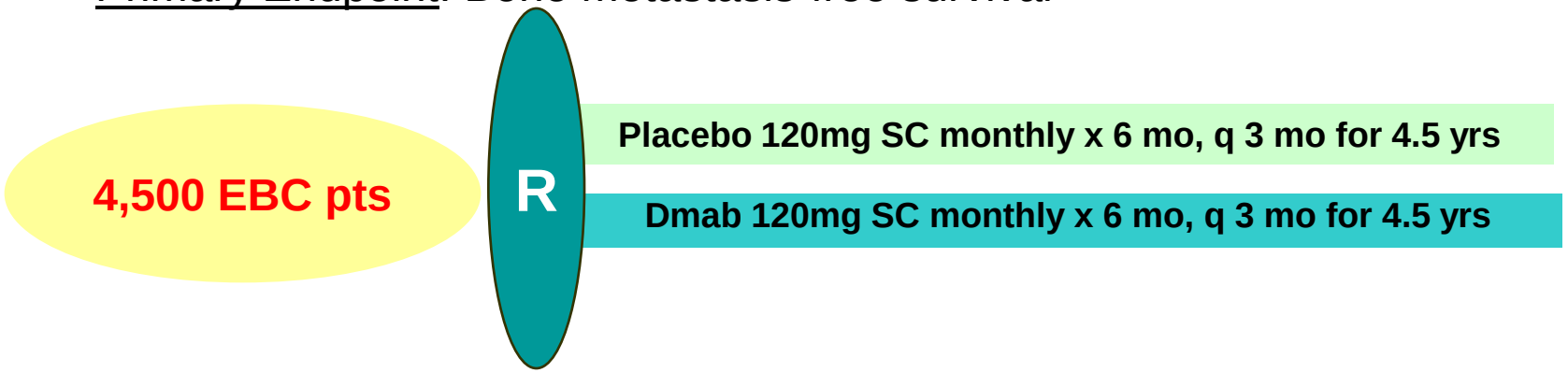
ABCSG-18:

- Primary Endpoint: Rate of 1st clinical fracture
- Secondary Endpoints: Bone metastasis-free survival (BMFS), DFS, OS



D-CARE:

- Primary Endpoint: Bone metastasis-free survival



Prevention Trials with Zoledronic Acid HOBOE (dal 2003)

Studio randomizzato di fase III sugli effetti ossei della terapia adiuvante del ca mammario con Tamoxifene, Letrozolo, e Letrozolo + Acido Zoledronico

Valutazione dell'efficacia di Letrozolo + Triptorelina e Letrozolo + Triptorelina + Acido Zoledronico nel trattamento adiuvante del ca mammario mammario endocrino-responsivo in pazienti in premenopausa

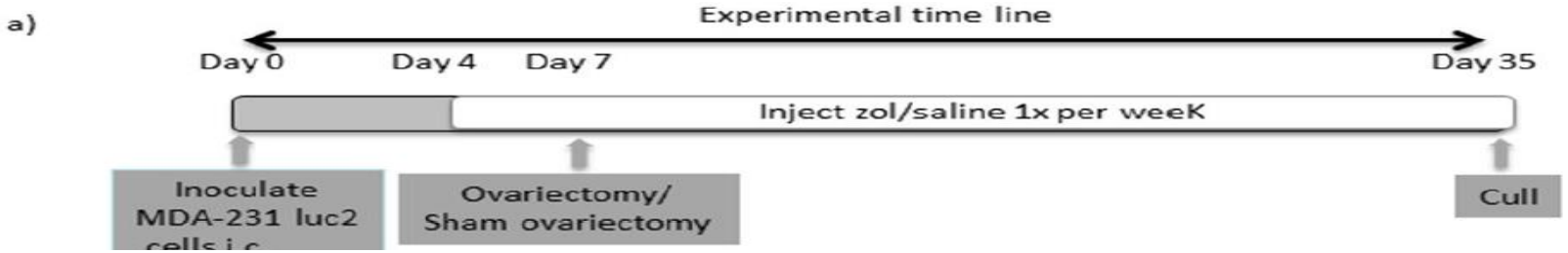
<u>Obiettivi in premenopausa (recettori positivi):</u>

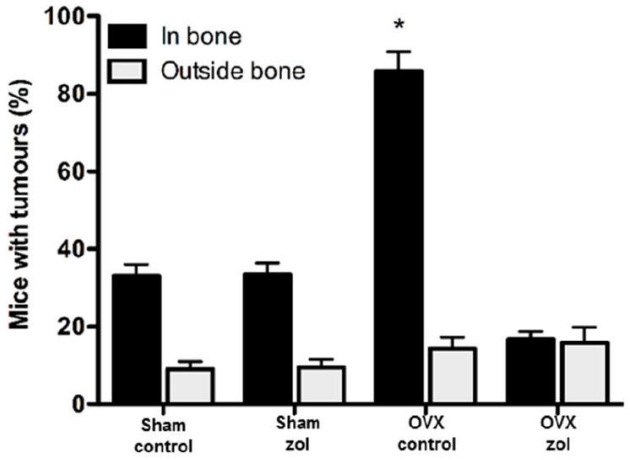
1. **DFS**
2. **altri indicatori di efficacia, tossicità, modifiche del profilo ormonale, BMD, Incidenza di Sdr metabolica, modifiche di biomarcatori sierici.**

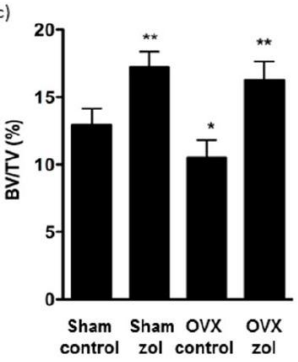
<u>Disegno dello studio:</u>

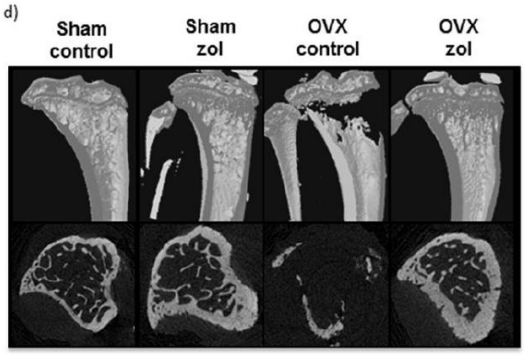
5 anni durata del trattamento ormonale, Zol 4 mg ogni 6 mesi per 5 aa

OVX increased bone resorption and induced growth of disseminated tumour cells in bone









Effects of OVX on tumor growth:
-Tumours were detected in 83% of OVX mice compared to 17% ctrl mice

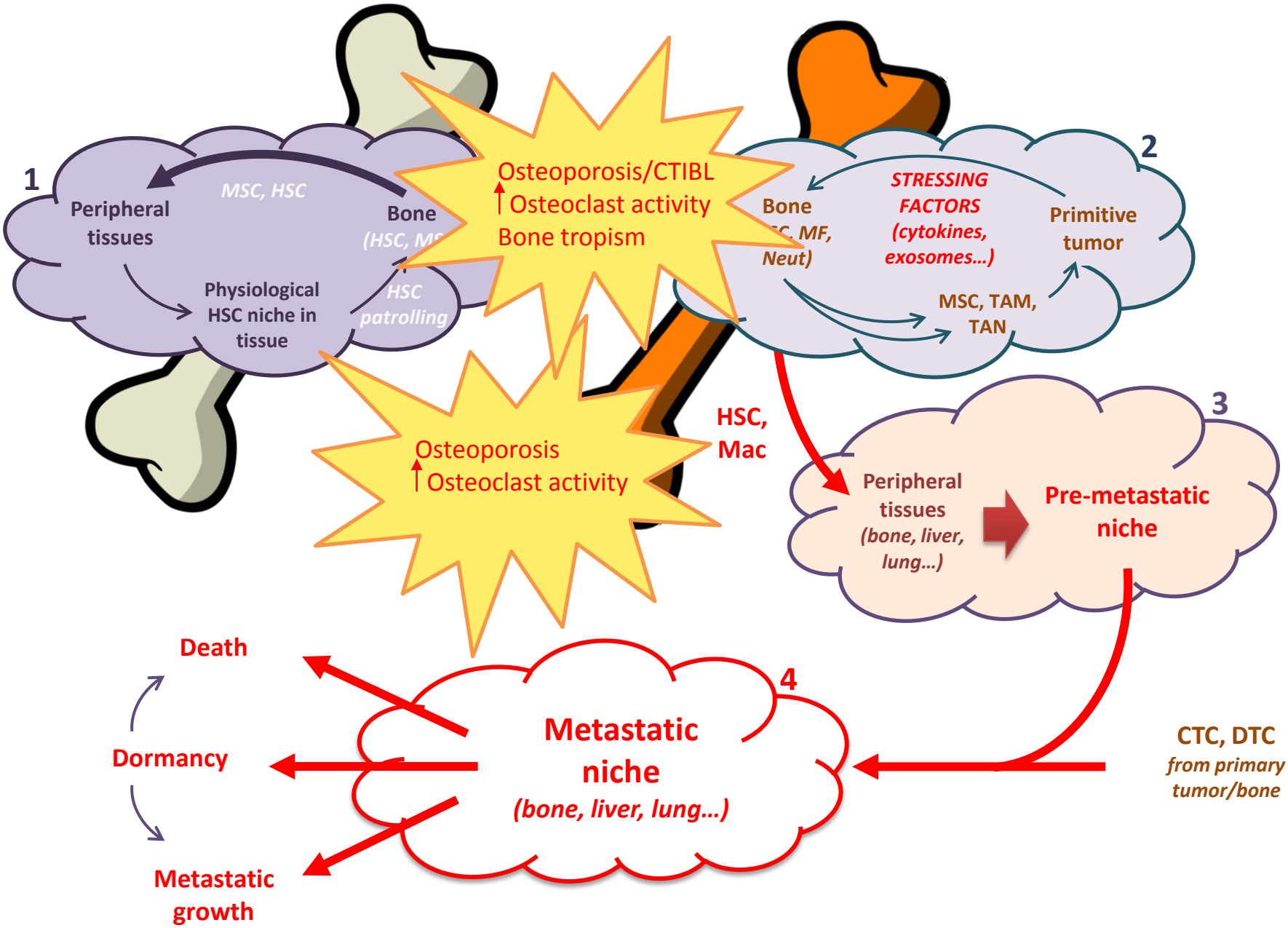
- OVX-induced tumour growth was completely prevented by ZOL

Effect of OVX on bone cells
- significant increase in expression of DKK1, RANKL, decrease of OPG;
-increased expression of proteolytic enzymes, including MMP-9 and Cathepsin K .

MMP9 & Cathepsin K
activate the bone marrow endosteal stem cell niche.

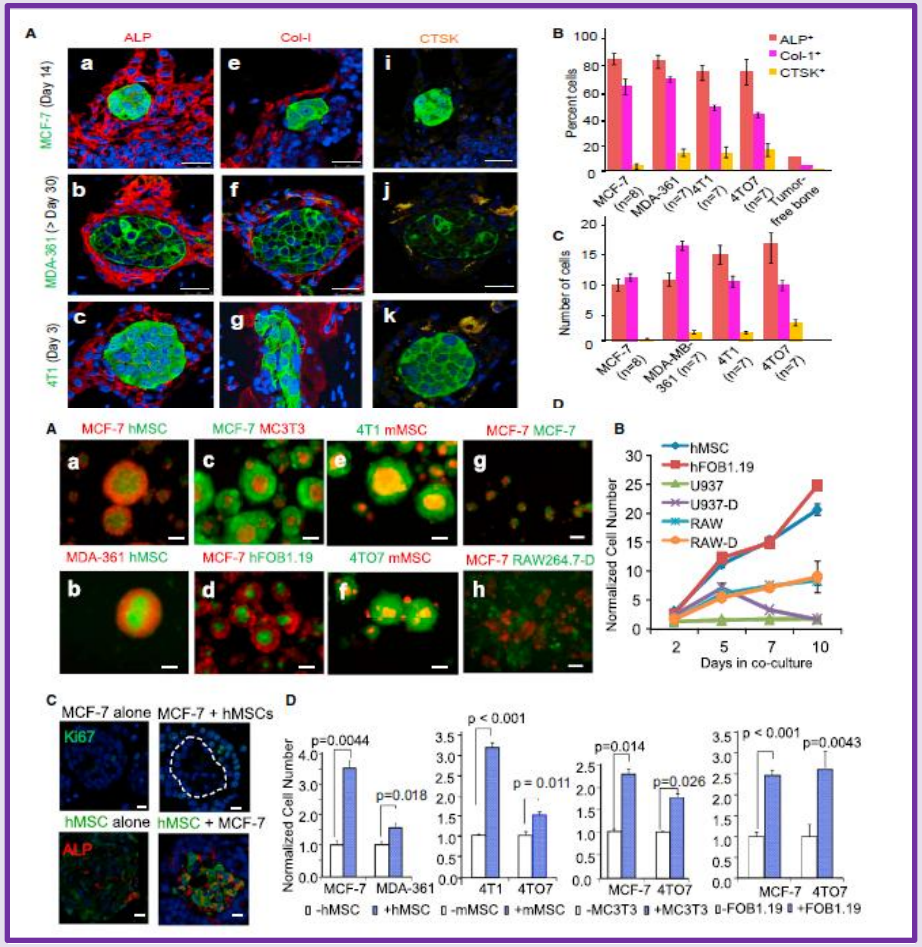
Ottewell, Clin Can Res 2014

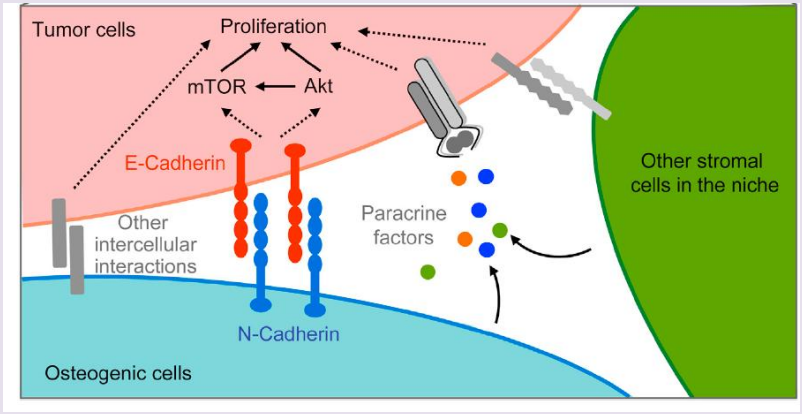
The Metastatic Process: hypothesis

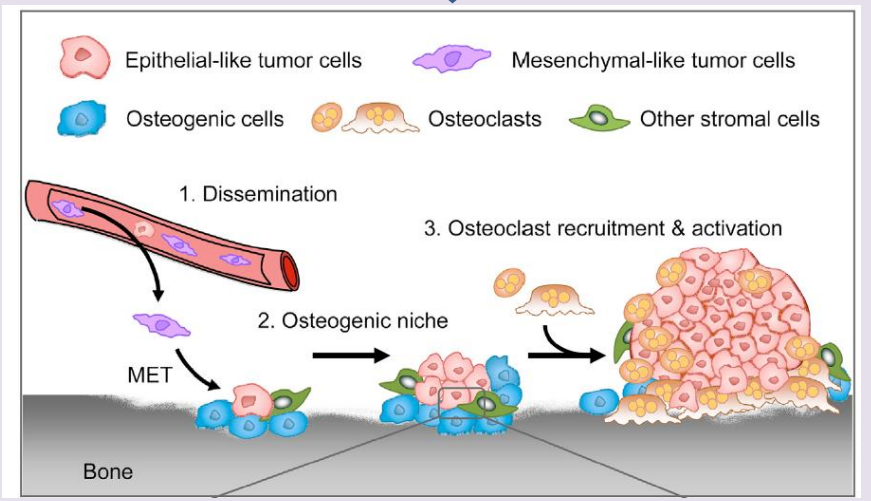


Ibrahim T, not pubblished

The Osteogenic Niche Promotes Early-Stage Bone Colonization of Disseminated Breast Cancer Cells







Wang, Cancer Cell 2015

Results

Table 3 Frequency of Marker-expressing Tumors

	NED Patients (n = 10)		Relapsed Patients						*P* BM vs NED	*P* BM vs VM
			Overall (n = 30)		VM (n = 10)		BM (n = 20)			
	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	Patients	Patients
OPG	20	(6-52)	23	(12-41)	20	(6-52)	25	(11-47)	1.000	1.000
RANK	20	(6-52)	17	(7-34)	0	0	25	(11-47)	1.000	.140
CXCR4	10	(0-29)	30	(14-46)	0	0	45	(23-67)	.101	.013

Abbreviations: BM = bone metastasis; CI = confidence interval; NED = no evidence of disease; VM = visceral metastasis.

❖The CXCR4+RANK combination was an independent predictive marker of relapse to bone, increasing the RR of bone relapse 9.3-fold in the BM group with respect to NED-VM patients (*P =0.*008).

❖Considering only patients who relapsed to viscera as control group, the RR of bone relapse increased 16.1-fold.

Ibrahim T, Clin breast cancer 2011

Mini-gene profiling: tissue markers in the prediction of bone metastases in breast cancer patients

Median values

Patients	b2m	ctgf	Hpse	sparc	tff1	tnfrsf11a	cxcr4	ibsp
BM 30	0.40	0.71	3.11	4.52	430.64	0.66	2.76	0.69
VM 30	0.19	0.41	1.76	1.74	99.51	0.28	2.02	0.87
NED 30	0.22	0.49	2.35	2.41	32.79	0.56	0.78	0.42

Sensitivity/ specificity

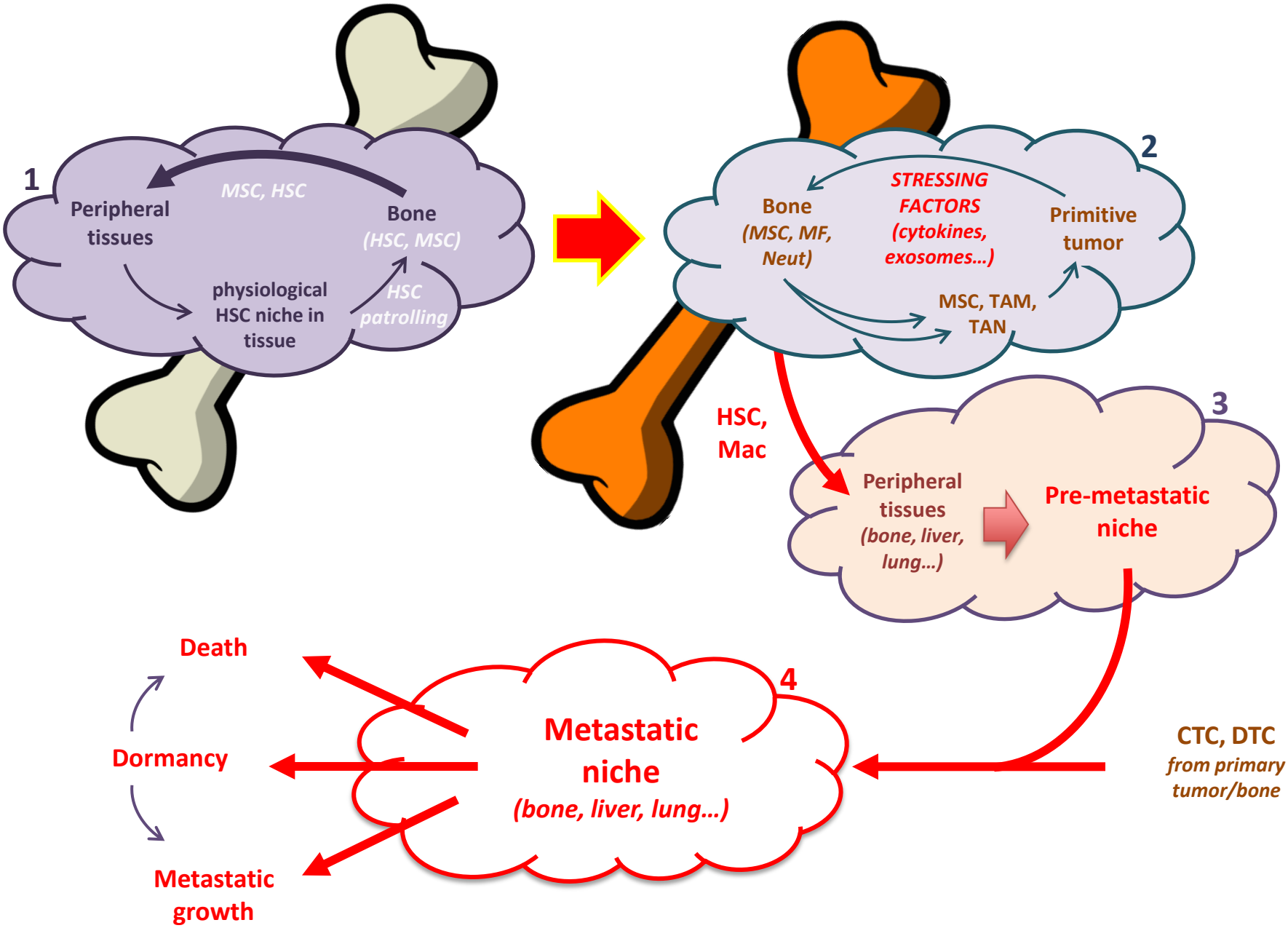
Marker	Sensitivity	Specificity vs VM	Specificity vs NEDP
B2m	27	94	100
CTGF	30	97	88
HPSE	18	97	96
SPARC	9	100	100
TFF1	63	79	77
RANK	18	100	96
CXCR4	35	100	87
IBSP	20	100	100

Unpublished data

Univariate analysis:

❑ TFF1 predicts in a statistical significant way the relapse/site of relapse

The Metastatic Process: hypothesis



Ibrahim T, not pubblished

Centro di Osteoncologia, IRST- Meldola
Ambulatorio CDO3 dedicato a CTIBL

Screening:

1- **dosaggio: creatinina, calcemia, PTH, 25OHvitD e CTX sierico, TSH reflex e densitometria ossea;**
2- **RX torace L o RX rachide DL (ricerca fratture morfometriche)**
3- **fattori di rischio**

Azioni

Linee Guida AIOM 2014

1- Agire sui fattori di rischio;
2- Calcio e vitamina D3
3- terapia con Bone Target Therapy
4- valutazione odontoiatrica (linee guida SIOMMMS/ANDI 2009).
4- Controllo regolare anche dell'assetto lipidico (Col, Trig.) e acido urico;
5- Controllo ogni 12 mesi: creatinina, calcemia, PTH, 25OHvitD e CTX sierico, TSH reflex e densitometria ossea ogni 18-24 m (criteri LEA, ipogonadismo, classe I)

A new emergency in oncology: Bone metastases in breast cancer patients. Ibrahim T, Mercatali L, Amadori D. Oncol Lett. 2013

Rapporto Cancro e Osso

EVOLUZIONE

Tumori primitivi → **le metastasi ossee e CTIBL**

RIVOLUZIONE:

- **Approccio multi e interdisciplinare: nascita dell'Osteoncologia**

- **Obiettivi: Prevenzione degli SRE e la storia naturale dei tumori (CTIBL)**

Centro di Osteoncologia e Tumori Rari CDO-TR

Responsabile:
Toni Ibrahim

Oncologi:
Nada Riva
Alberto Bongiovanni
Sebastiano Calpona
Federica Recine
Davide Bruschi

Specializzandi:
Giulia Marcantognini
Valentina Fausti

Infermiera:
Venetia Zavoiu

Farmacista:
Valentina Di Iorio

Grazie

Ricercatori di base:
Laura Mercatali (PI)
Chiara Liverani
Alessandro De Vita
Chiara Spadazzi
Federico La Manna
Giacomo Miserocchi

Data Manager:
Manuela Monti
Patrizia Serra

Statistico:
Flavia Foca