



VII CONGRESSO NAZIONALE
SOCIETÀ ITALIANA DI OSTEONCOLOGIA
20-21 OTTOBRE 2022 ROMA



CON IL PATROCINIO DI



SAPIENZA
UNIVERSITÀ DI ROMA



**SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA**
Istituto Ortopedico Rizzoli di Bologna
Istituto di Ricovero e Cura a Carattere Scientifico



***L'Osteoncologia:
Dalla multidisciplinarietà alla
medicina personalizzata***

Toni Ibrahim BSc, MSc, MD, PhD

***Direttore SC Osteoncologia, Sarcomi dell'Osso e
dei Tessuti molli e Terapie innovative (OSOTT)
Coordinatore percorsi, Reti e Ricerca Oncologica IOR (CRRO)***

IRCCS- Istituto Ortopedico Rizzoli, Bologna

Roma, 20/10/2022

25 years with Prof Dino Amadori....Thanks...



Gen 1996- Gen 2020

With Prof Amadori...

Fellow of Istituto Oncologico
Romagnolo and
part of Breast Group

2000

Promotion of the Multidisciplinary
National Project of Osteoncology

Gen 2005

Osteoncology Center

Oct 2011

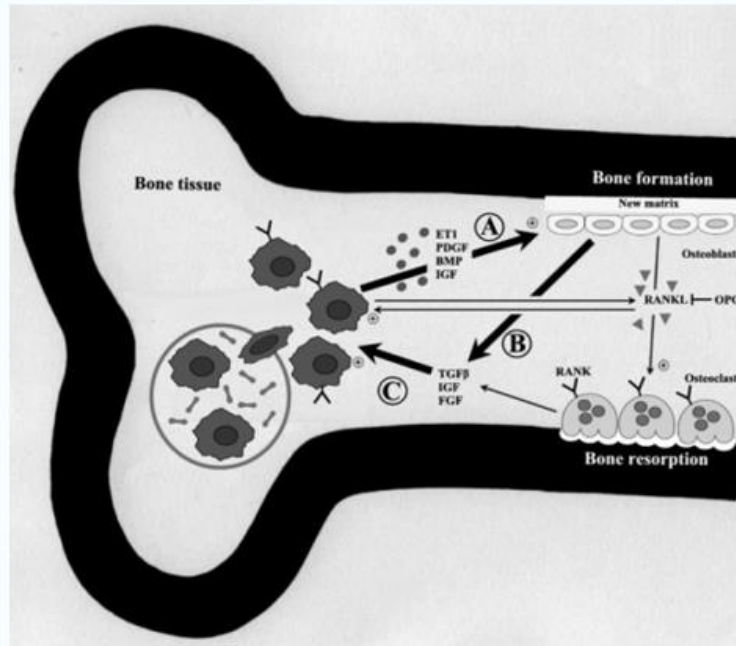
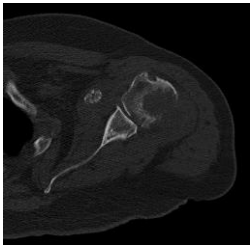
Osteoncology
and Rare Tumors Center

Aprile 2020

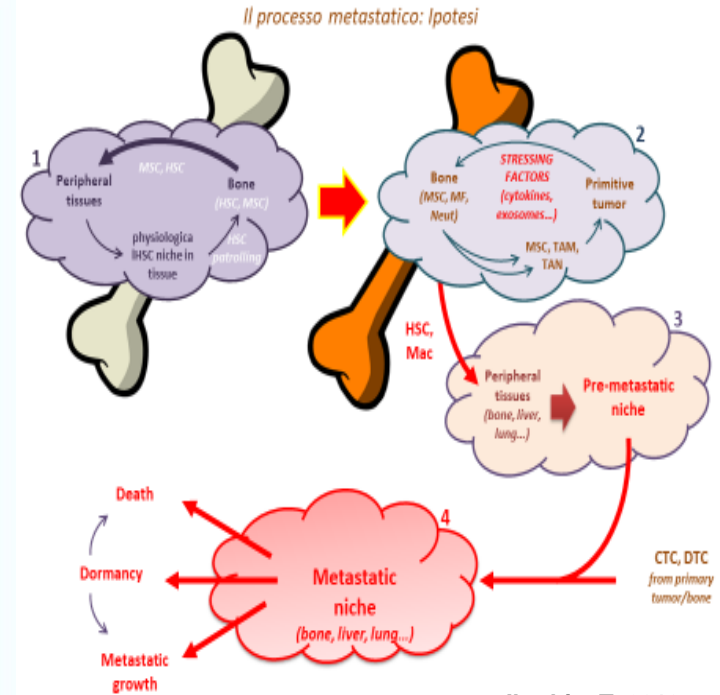
Osteoncology, Rare Tumors and
Immuno-Gene Therapy Unit



The Osteoncology



Ibrahim T, Cancer 2010



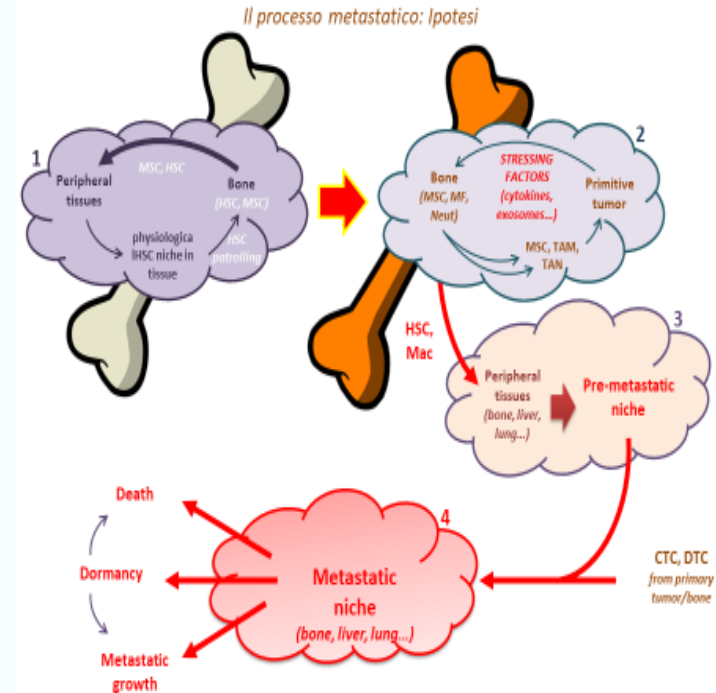
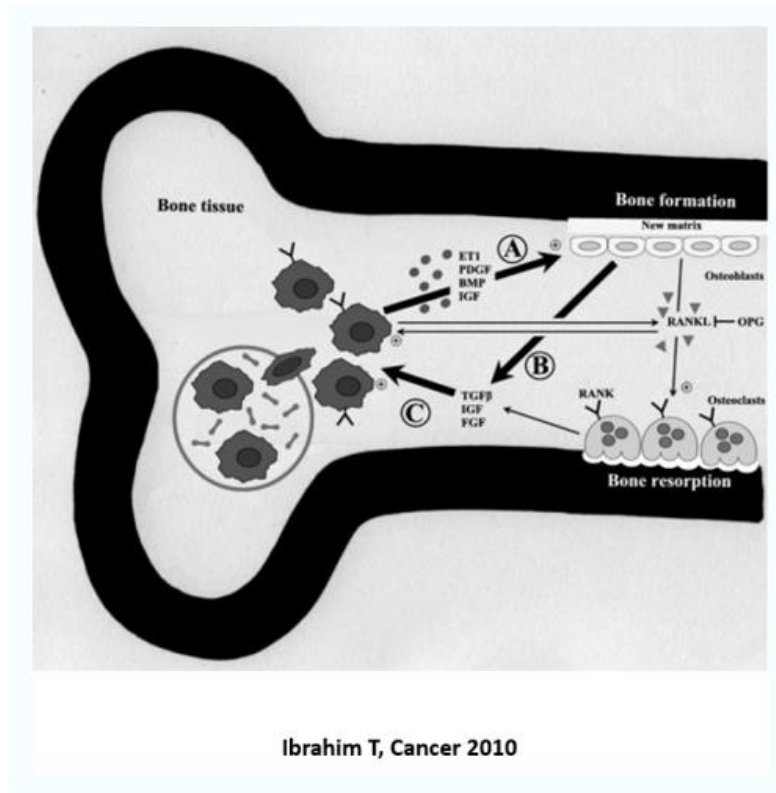
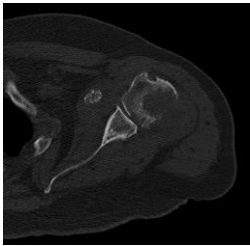
Ibrahim T, 2018

2000

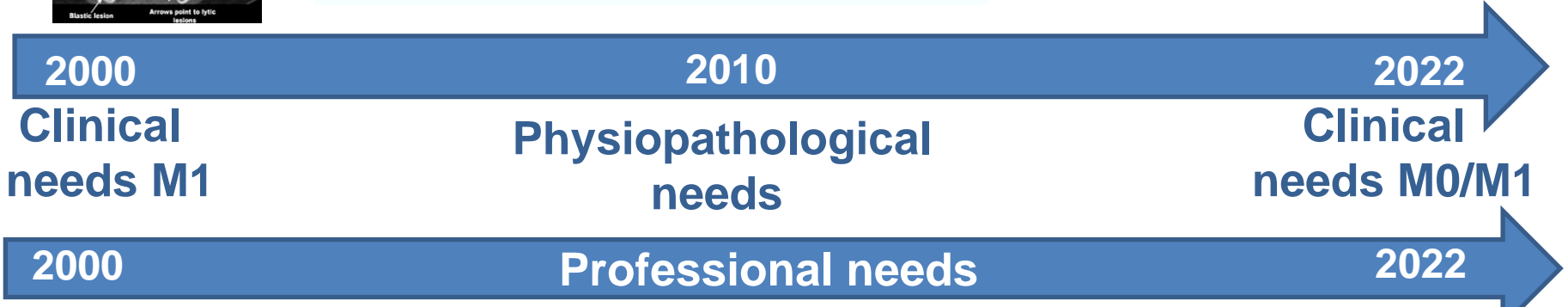
2010

2022

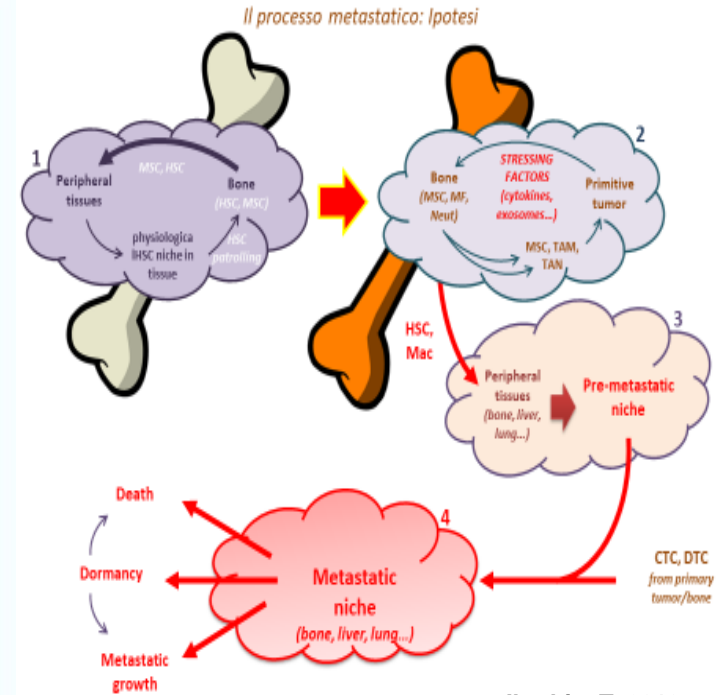
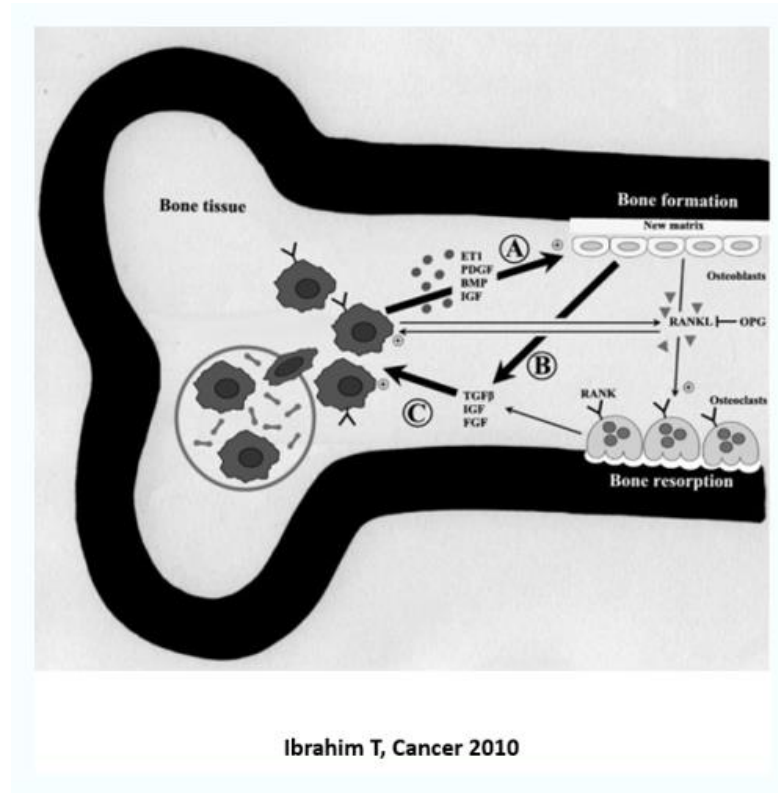
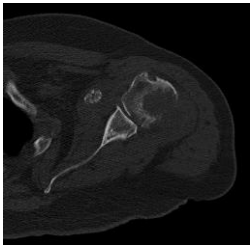
The Osteoncology



Ibrahim T, 2018



The Osteoncology



2000

**Clinical
needs M1**

2010

**Physiopathological
needs**

2022

**Clinical
needs M0/M1**

2000

Professional needs

2022

Bone Metastases

Responsible for high morbidity in patients with cancer for two reasons:

- Epidemiological

- Clinical

INCIDENCE

Tumor type

Age

A
Re
All

1

Frequency of serious complications depends on:

- Tumor site: more frequent in sites under dynamic stress, e.g. femur.
- Lesion type: more frequent in lytic than in blastic lesions.
- Treatment, especially preventive

Amadori D, Ibrahim T, Osteoncologia, Ed. Exc. Med. 2003

arrow suppression

U, Ibrahim T, Osteoncologia, Ed. Exc. Med. 2003



Oncologist

**Dedicated
Nurse**

Radiotherapist

**Orthopedic
Specialist**

**Neurological
surgeon**

**Palliative Care
Expert**

Radiologist

**Nuclear Medicine
Physician**

Physiatrist

Psicologist

Endocrinologist

**Clinical
Pathologist**

Pathologist

Data Manager

Lab Reasearchers

**The Osteoncology
model
with the patient**



Prof. Dino Amadori

OSTEONCOLOGY: New discipline in Oncology

2000 **Italian Project: Multidisciplinary approach to Bone Metastases** **2022**

National training courses

2002 Bologna, Rome 2003 Naples, Bologna 2004 Naples, Florence

Publications: 3 books

2003 - 2021

National training and practical courses in Osteoncoology
(Modena – Forlì- Meldola- Roma- Verona- others)

Course
in Osteoncoology

2003 - 2005

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

Masters/PhD
in Osteoncoology

2009-2021

PhD in Osteoncoology (Campus Biomedico Roma)

Establishment of
Osteoncoology
field

Establishment of
Osteoncoology
Center



**National Bone
Metastases
Data Base**

**Multidisciplinary
Osteoncoology
School (MOS)**



National Osteoncology Network

www.osteoncology.it

Centri accreditati di eccellenza:

- Centro di Osteoncologia presso l'istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRCCS di Meldola
- Centro di Osteoncologia presso l'istituto Oncologico Veneto IOV
- Centro di Osteoncologia presso l'istituto Tumori Regina Elena, Roma
- Centro di Osteoncologia presso l'Università Campus Biomedico, Roma

Centri che rispettano i requisiti minimi:

- Centro di Osteoncologia presso l'istituto Neurotraumatologico Italiano, Grottaferrata (RM)
- Centro di Osteoncologia presso Ospedale Gradenigo (TO)



Italian Society of Osteoncology

18 July 2008

Mission

Care

Promotion of multidisciplinary team to follow and treat patients with cancer bone disease (primitive and bone metastases, CTIBL).

Research

Promotion of basic, translational and clinical multidisciplinary research in the field of Osteoncology.

Training

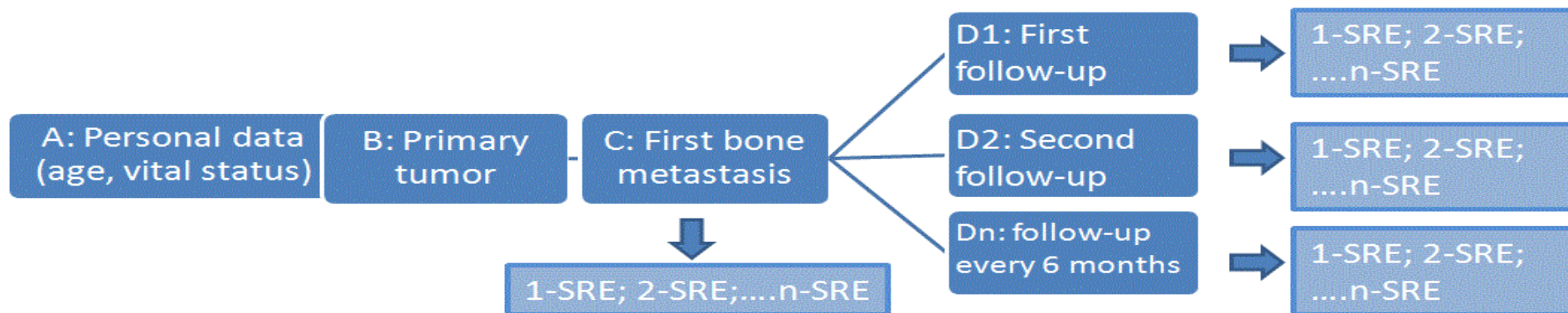
Promotion of the training in the Osteoncology discipline.

National Bone Metastases Data Base (2014)

Materials and Methods



BM Data Base is a multicenter prospective observational study, which has as Coordinating Center (CC), IRCCS IRST of Meldola. The database will allow to gather information on the medical history of patients with BM using an online software tailored for these data.



The data are updated every 6 months by the participating centers and reviewed by CC.

Multidisciplinary Osteoncology School

MOS 2016 IRST-IRCCS, Meldola

Mission

**Promote training in Osteoncology
(bone metastases/bone health):**

- Mono- and multidisciplinary care**
- Basic, translational and clinical research**
- Integration between assistance and research**

Target

All professionals interested in Osteoncology from lab to the assistance

Treatment of Bone Metastases

Treatment of Bone Metastases

Medical treatment

- ✓ Chemotherapy
- ✓ Endocrine therapy
- ✓ Bio-immunotherapy
- ✓ Bone target therapy:
 - Bisphosphonates
 - RANK-L antibody (denosumab)
 - Cathepsin K inhibitor
 - Src inhibitor
 - PTH-rP antibody
 - CXCR-4 antagonist
 - HDAC inhibitors
 - Proteosome inhibition
 - Anti-integrin
 - TGF- β inhibitors
 - ETRA inhibitor
 - Wnt inhibitor
- ✓ Palliative care:
 - Analgesic drugs
 - Best Supportive Care

Radiotherapy

Radiometabolic treatment

Orthopedic surgery

Interventional radiology

Rehabilitation

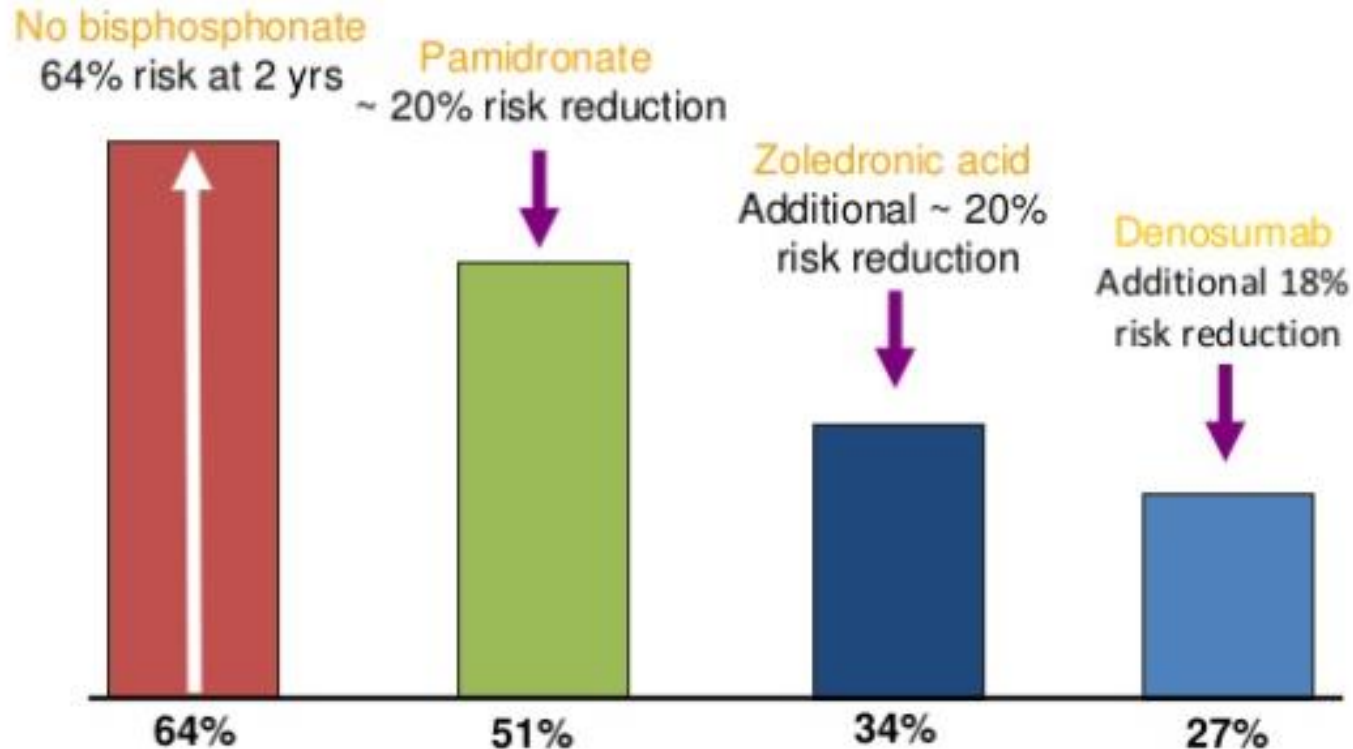
RANK-L, receptor activator of nuclear factor-kb ligand; PTH-rP, parathyroid hormone-related peptide; CXCR-4, chemokine receptor type 4; HDAC, histone deacetylase; TGF- β , tumor growth factor β ; ETRA, endothelin receptor A

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

✓ well known antitumor agents

✓ Bone targeted agents =
Bone modifying agents

Skeletal Complication Risk: Incremental Benefits in Breast Cancer



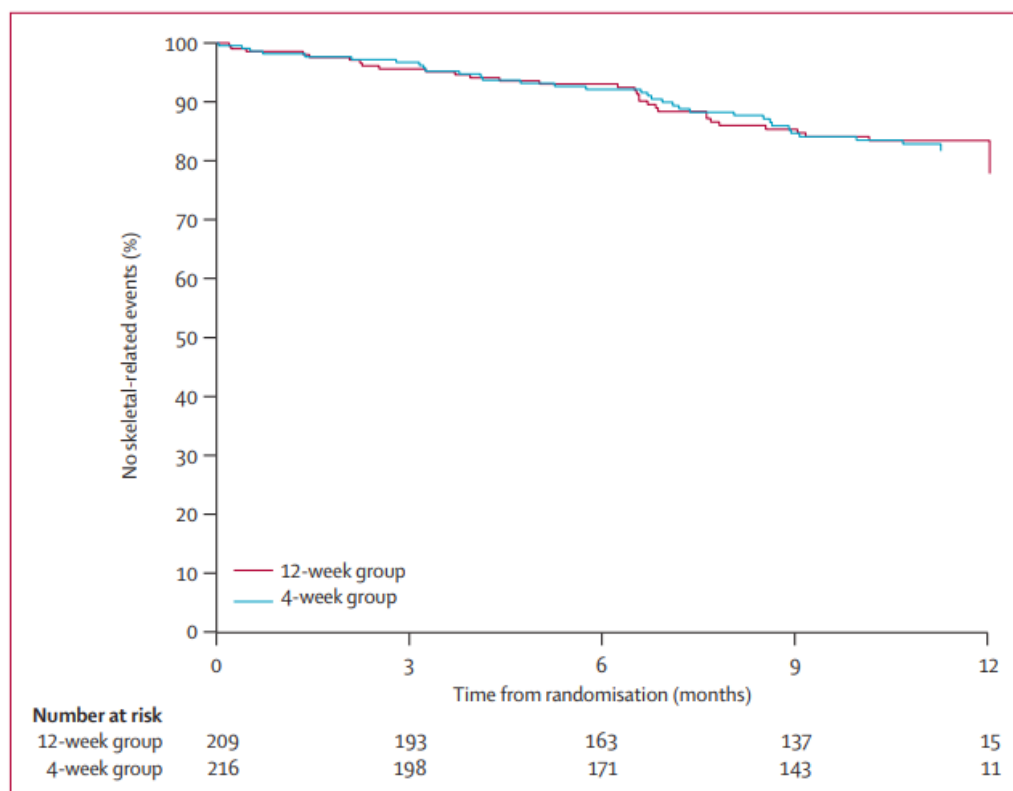
Lipton A, et al. Cancer. 2000;88:3033-3037. Rosen LS, et al. Cancer. 2003;100:36-43. Stopeck A, et al. ECCO/ESMO 2009. Abstract 2LBA. Stopeck AT, et al. J Clin Oncol. 2010;28:5132-5139.

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



Dino Amadori, Massimo Aglietta, Barbara Alessi, Lorenzo Gianni, Toni Ibrahim, Gabriella Farina, Fernando Gaion, Francesco Bertoldo, Daniele Santini, Roberta Rondena, Paola Bogani, Carla I Ripamonti

Lancet Oncol 2013





Linee guida METASTASI OSSEE E SALUTE DELL'OSSO

Edizione 2022

In collaborazione con



Associazione Italiana di Medicina Nucleare
e Imaging Molecolare



Associazione Italiana
Radioterapia e Oncologia clinica



Società Italiana di
Osteoncologia



Società Italiana di Anatomia Patologica
e Citologia Diagnostica - Divisione Italiana
della International Academy of Pathology



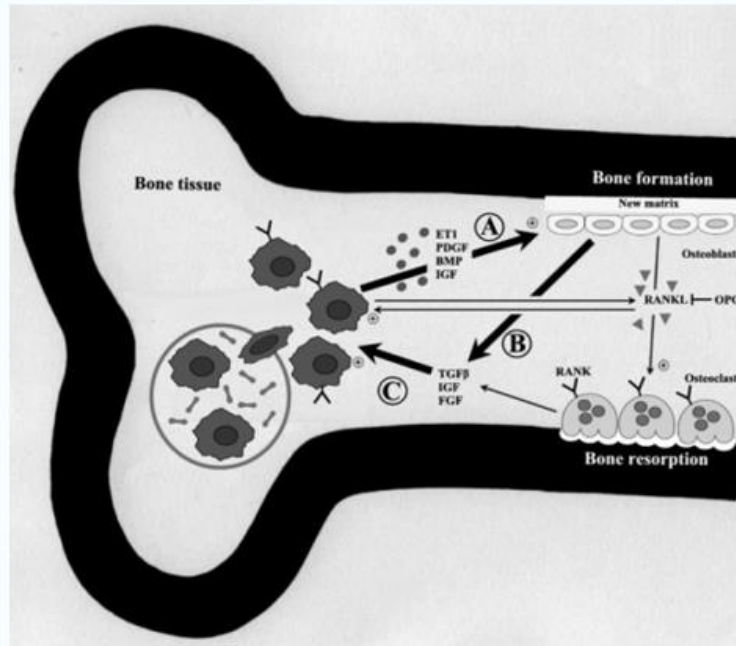
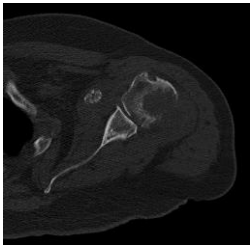
Società Italiana di
Radiologia Medica
e Interventistica



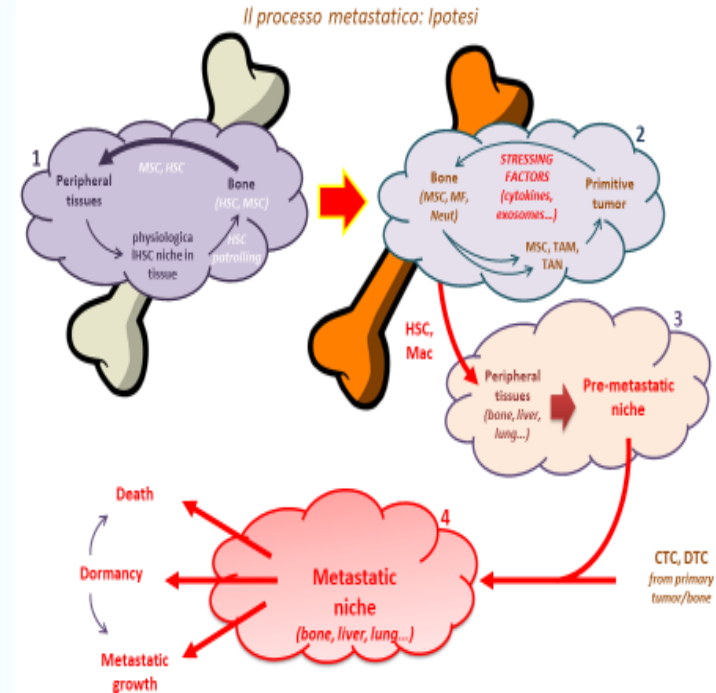
SOCIETÀ ITALIANA
DI ORTOPEDIA
E TRAUMATOLOGIA



The Osteoncology



Ibrahim T, Cancer 2010



Ibrahim T, 2018

2000

2010

2022

Clinical
needs M1

Physiopathological
needs

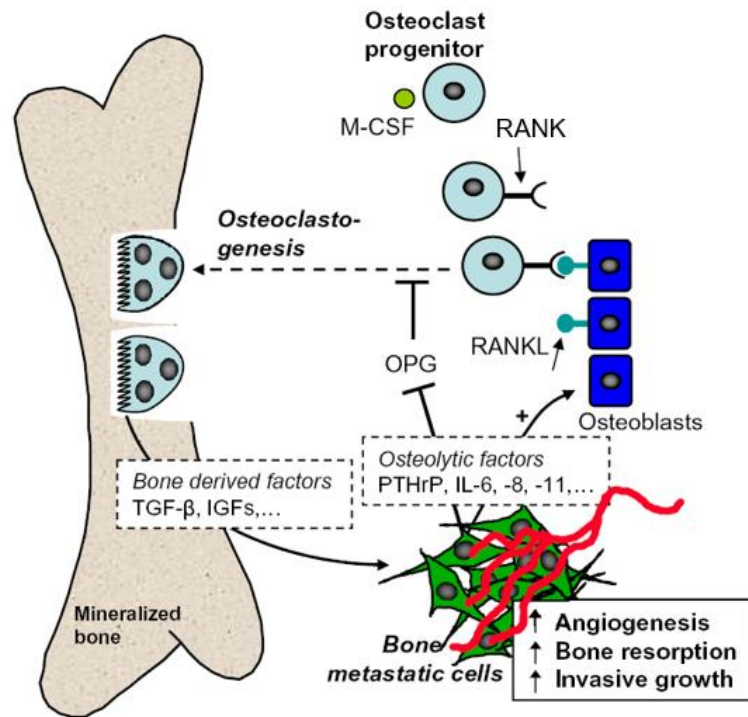
Clinical
needs M0/M1

2000

Professional needs

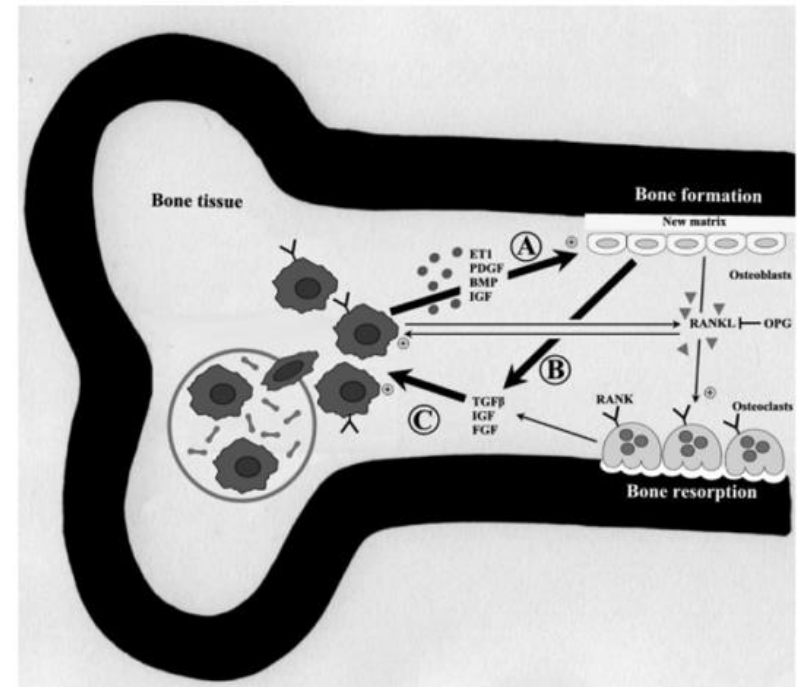
2022

OSTEOLYTIC MODEL: a vicious cycle

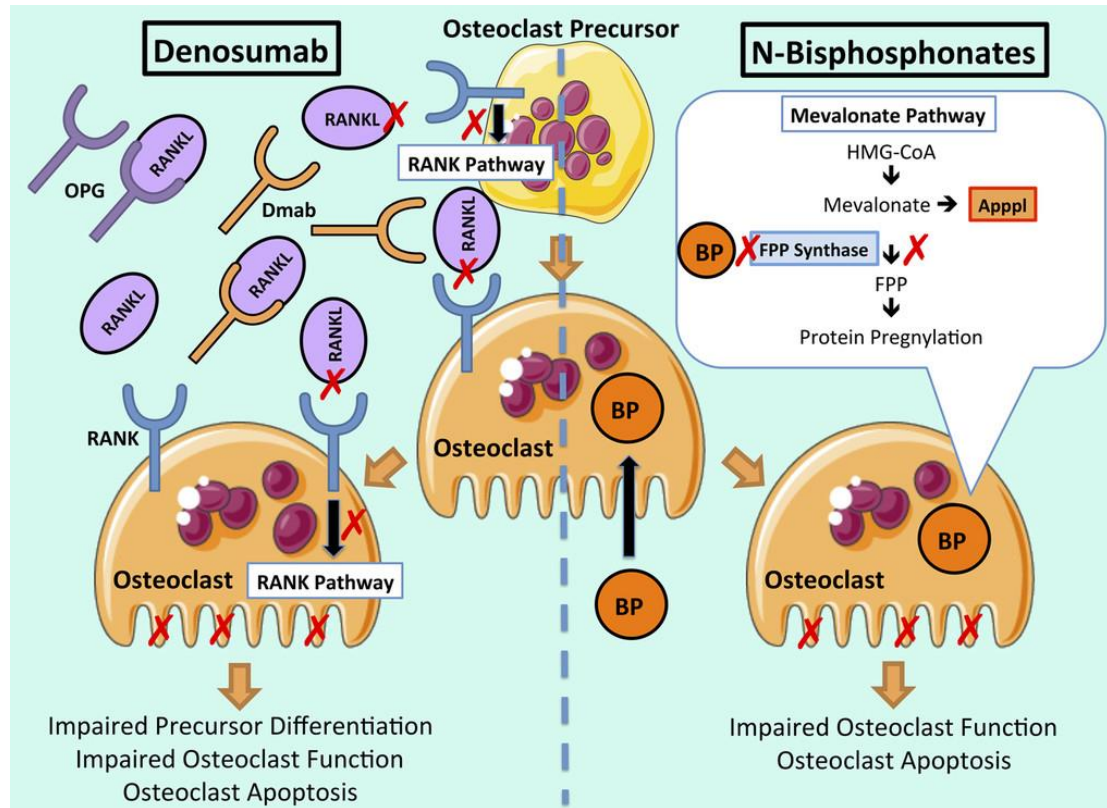


Buijs, The prostate, 2009

OSTEOBLASTIC MODEL: a vicious cycle

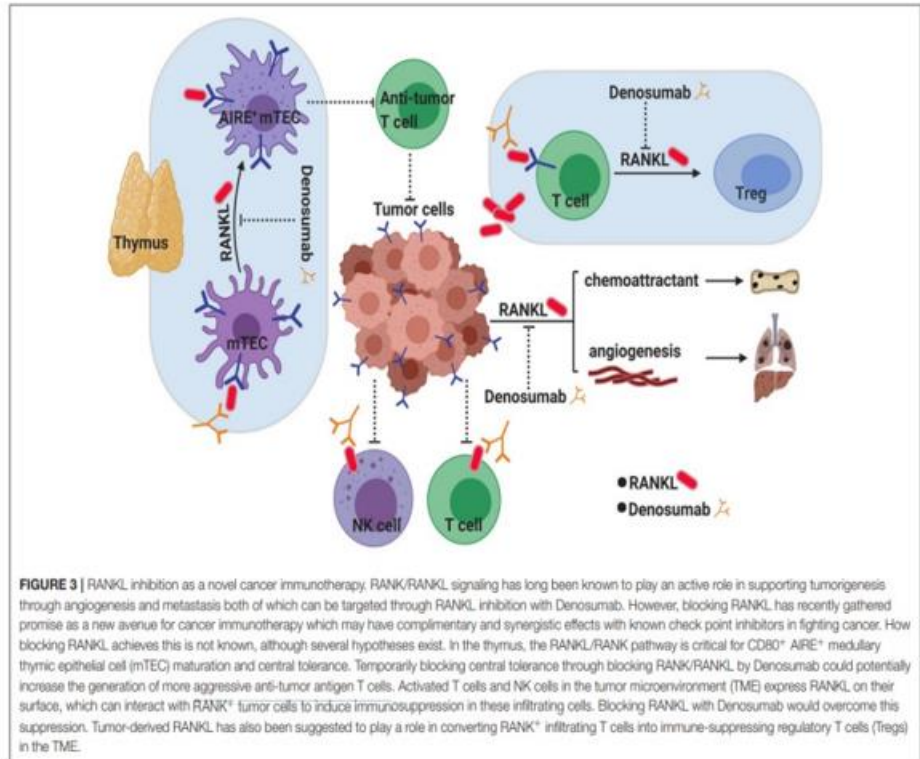


Ibrahim T, Cancer 2010



Preclinical antitumor profile of bisphosphonates

- Inhibition of cancer cell adhesion to extracellular matrix proteins
(Pluijm *et al.*, J Clin Invest, 1996; Boissier, & Clézardin, Cancer Res, 1997; then others)
- Inhibition of cancer cell proliferation and induction of apoptosis
(Shipman *et al.*, Br J Haematol, 1997; then others)
- Inhibition of cancer cell migration and invasion
(Boissier, & Clézardin, Cancer Res, 2000; then others)
- Stimulation of the expansion of human $\gamma\delta$ T cells
(Kunzmann *et al.*, Blood, 2000; then others)
- Inhibition of angiogenesis
(Fournier, & Clézardin, Cancer Res, 2002; Wood *et al.*, JPET, 2002; then others)



Evolving cancer–niche interactions and therapeutic targets during bone metastasis

Reviews Nature 2021

Robert L. Satcher¹ and Xiang H.-F. Zhang^{2,3,4}

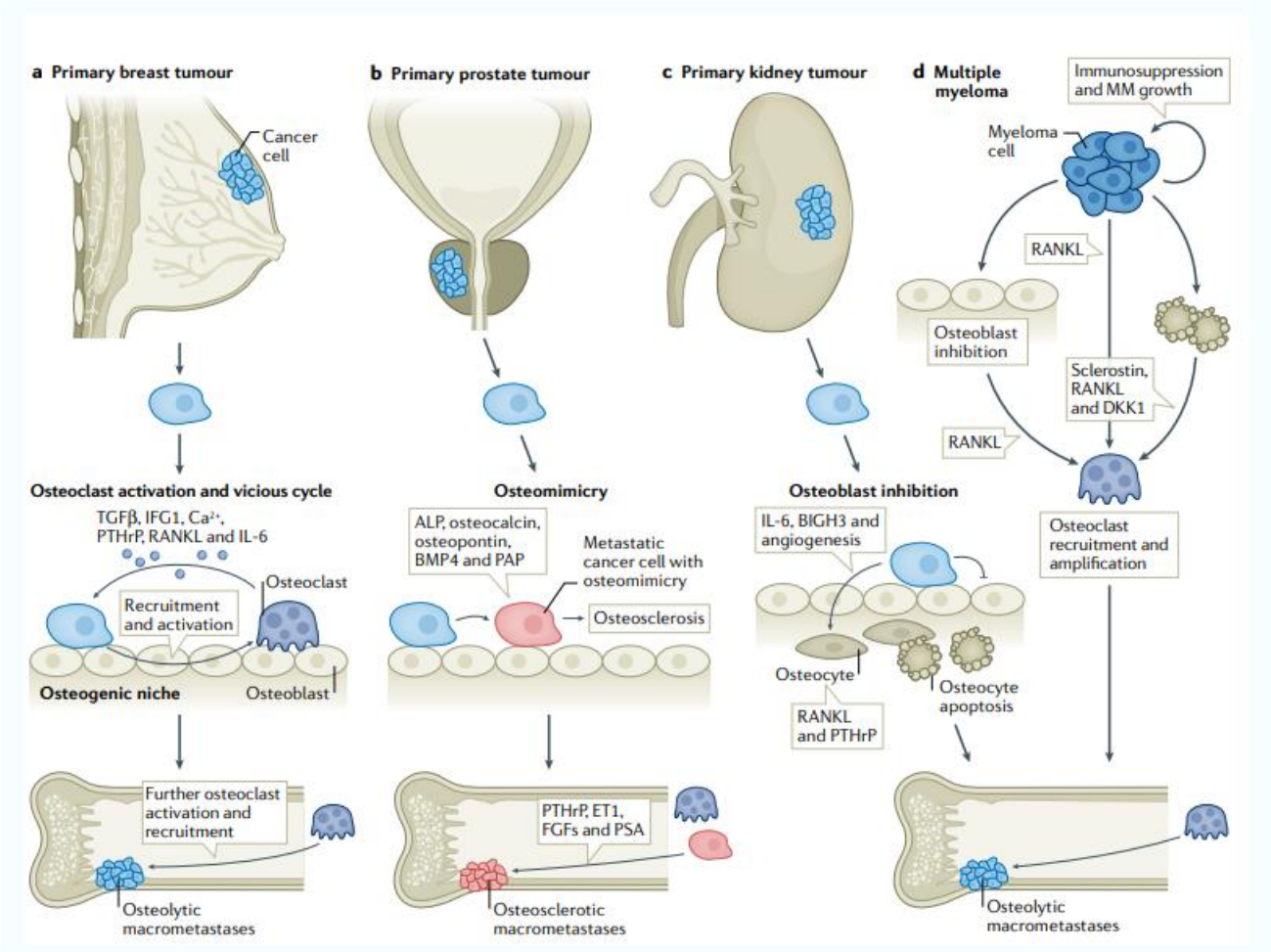


Fig. 3 | The relationship between primary tumour and the vicious cycle of late-stage bone metastasis in various cancer types. **a** | For breast cancer, disseminated tumour cells (DTCs) awaken from dormancy to create osteolytic macrometastases by both paracrine and heterotypic heterotypic adherens junction and gap junction interactions in the osteogenic niche, which directly and indirectly stimulate osteoclast recruitment and activation. Osteoclast activity, in turn, releases TGFβ, IGF1, Ca²⁺ and other growth factors from bone that further stimulate tumour proliferation. This is the classic ‘vicious cycle’. **b** | For prostate cancer, osteomimicry of DTCs in the osteogenic niche harnesses both the anabolic and lytic components of normal bone homeostasis, leading to osteolysis (PSA) and/or osteosclerosis (PAP). Tumour cells induce osteosclerosis via secretion of osteogenic factors such as ALP, osteocalcin, osteopontin and bone morphogenic protein 4 (BMP4). Osteolysis is induced via secretion of PTHrP, ET1 and IGF1. This global alteration towards bone-like phenotypes may be driven by RUNX2. The underlying genomics of osteomimicry and why it is not as predominant in other tumour types are not known. **c** | For kidney cancer, the road to bone destruction is more indirect

than for breast or prostate cancer, and resembles that for multiple myeloma (MM). DTCs create a vicious cycle via paracrine inhibition of osteoblast function and osteocyte apoptosis. Consequently, the adverse impact on the anabolic component of the osteogenic niche creates an environment that increases the RANKL to OPG ratio, promoting osteoclast recruitment and activity that creates predominantly lytic macrometastases. The details of interactions in the perivascular and osteogenic niches are likely tightly linked, as neovascular induction is a prominent component of kidney cancer bone metastasis. **d** | MM is almost exclusively bone organotropic. Interactions in the osteogenic niche are driven by crosstalk between MM cells and osteocytes, osteoblasts and osteoclasts. Osteolysis is induced via secretion of RANKL by MM cells, and amplified by RANKL from apoptotic osteocytes and inhibited osteoblasts. Immunosuppression enabling MM proliferation and progression is provoked by immune dysregulation, influencing T cell immunity, natural killer cell function and the antigen-presenting capacity of dendritic cells; and via myeloid derived suppressor cell amplification by osteoclasts. DKK1, Dickkopf-related protein 1.

Evolving cancer–niche interactions and therapeutic targets during bone metastasis

Reviews Nature 2021

Robert L. Satcher¹ and Xiang H.-F. Zhang^{2,5,4}

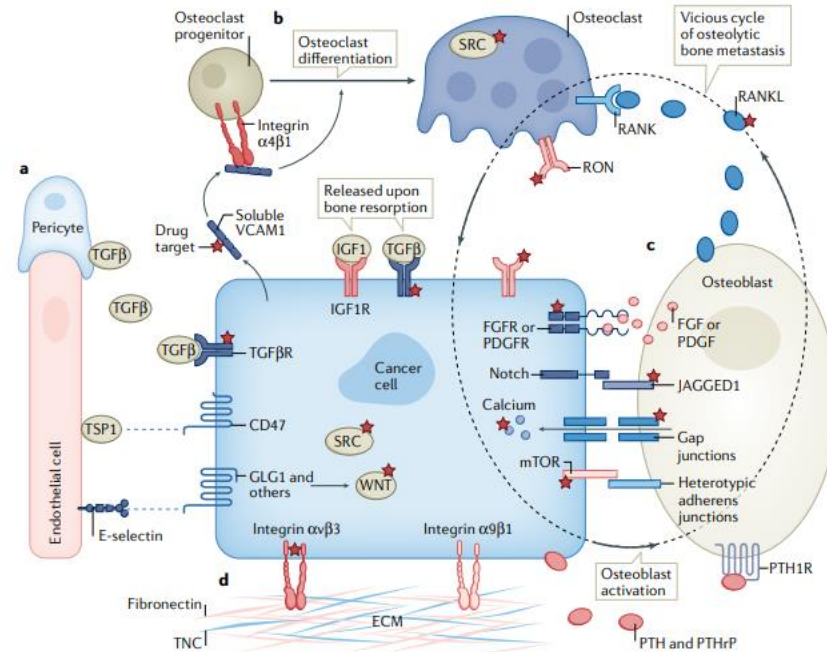
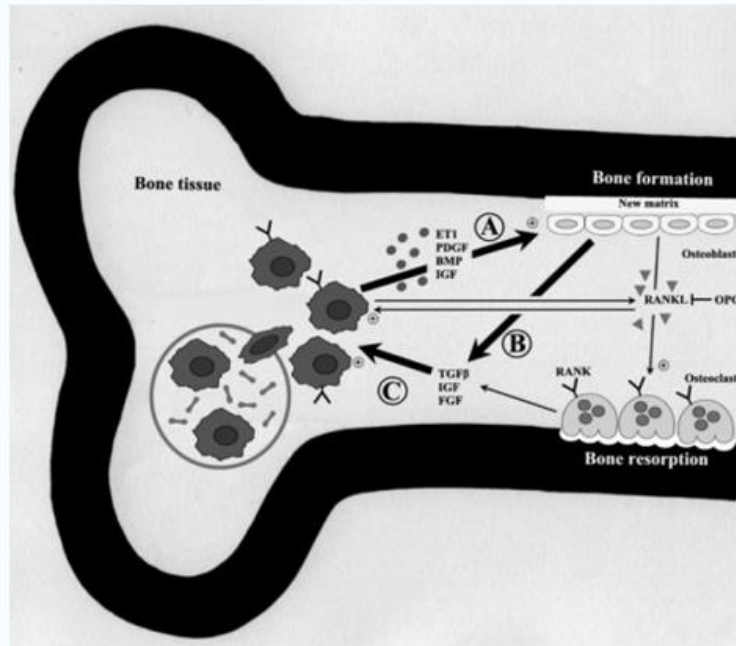
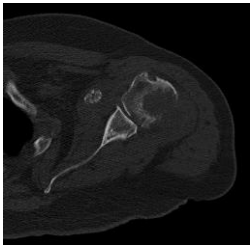
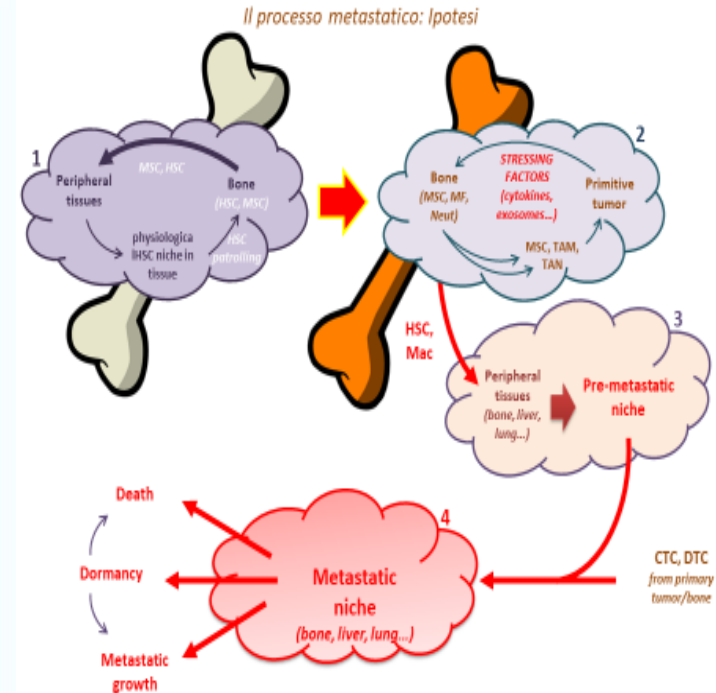


Fig. 4 | Emerging therapeutic targets in bone metastasis. **a** | Molecular crosstalk between cancer cells and perivascular niche cells including endothelial cells and pericytes. **b** | Therapeutic targets in differentiation of osteoclast progenitor cells into mature osteoclasts. **c** | Direct cell–cell interactions and paracrine between cancer cells and osteogenic cells. **d** | The integrin pathways mediating interaction between cancer cells with extracellular matrix (ECM) during bone metastasis. The dotted circle indicates the paradigm of vicious cycle that includes secretion of PTH and PTHrP by cancer cells that activates osteoblasts, the secretion of RANKL by osteoblasts that drives osteoclast differentiation and the release of TGFβ and IGF1 from bone matrix upon bone resorption that reciprocally promotes cancer cell progression. Molecules with targeted therapies available are highlighted with red stars. TNC, tenascin.

The Osteoncology



Ibrahim T, Cancer 2010



Ibrahim T, 2018

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Clinical
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2010

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2022

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needs M0/M1

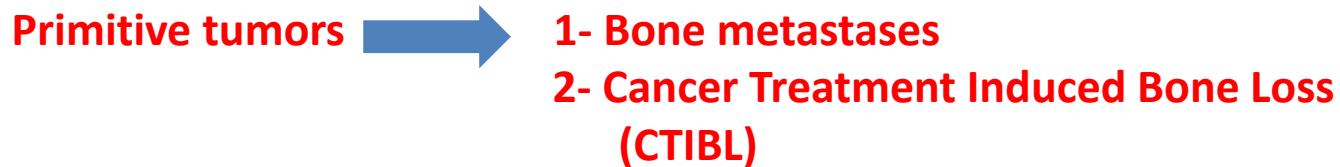
2000

Professional needs

2022

New Bone- Cancer relationship

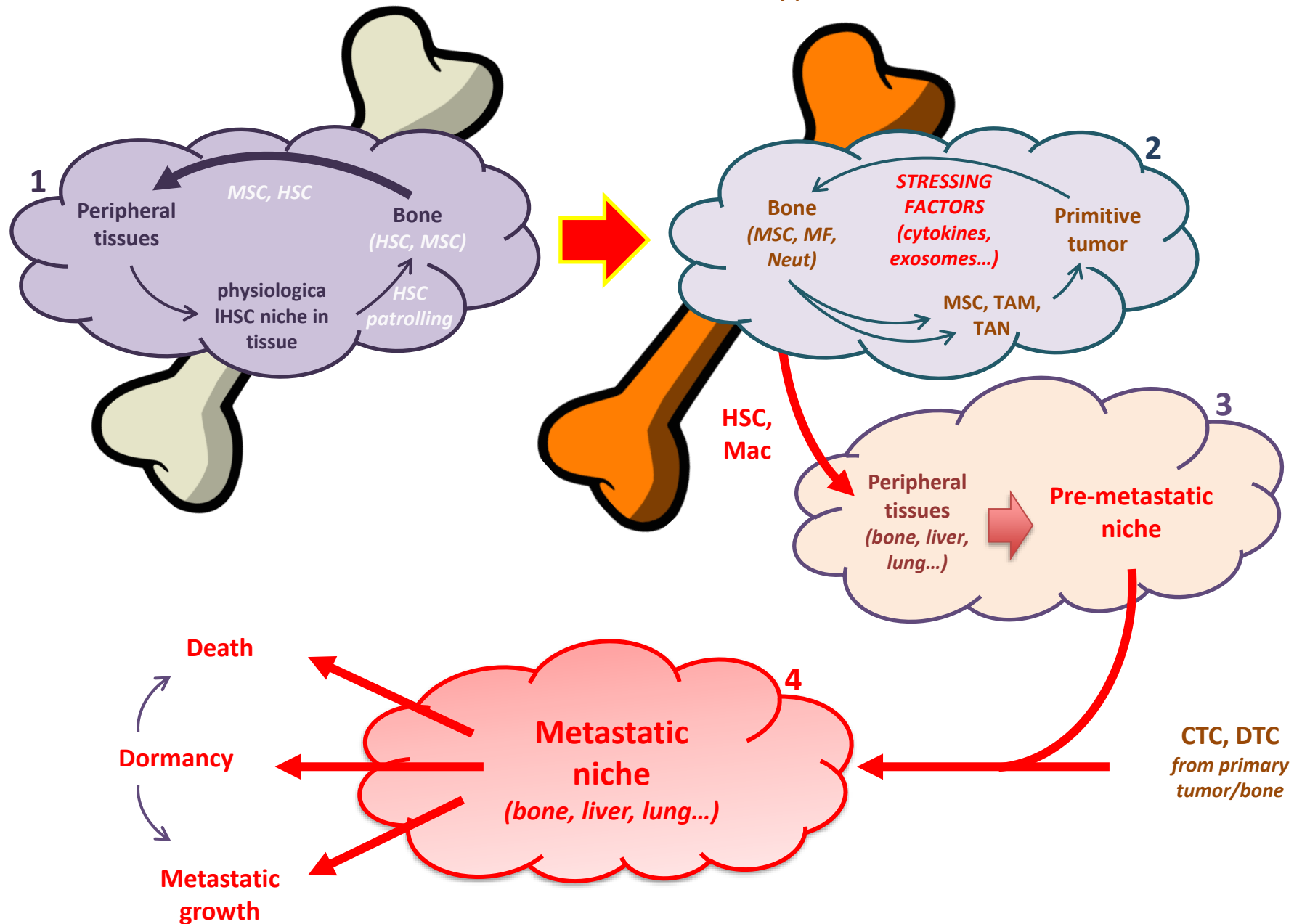
EVOLUTION



REVOLUTION

- Foundation of a new field in Oncology: **OSTEONCOLOGY**
- **Care:** mono and multidisciplinary approach
- **Research:** thanks to new Knowledge in the pathogenesis of bone metastases, on 2018 the aim of treatments is not only to prevent SREs, but also to have an impact in the natural history of cancer.

The Metastatic Process: hypothesis



Bone tropism

IRST DATA: RANK expression in primary breast cancers of patients with/without bone relapse

	NED Patients (n = 10)		Relapsed Patients				<i>P</i> BM vs NED Patients	<i>P</i> BM vs VM Patients		
			Overall (n = 30)		VM (n = 10)				BM (n = 20)	
	%	(95% CI)	%	(95% CI)	%	(95% CI)			%	(95% CI)
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	(2-29)	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 ($P=0.008$).

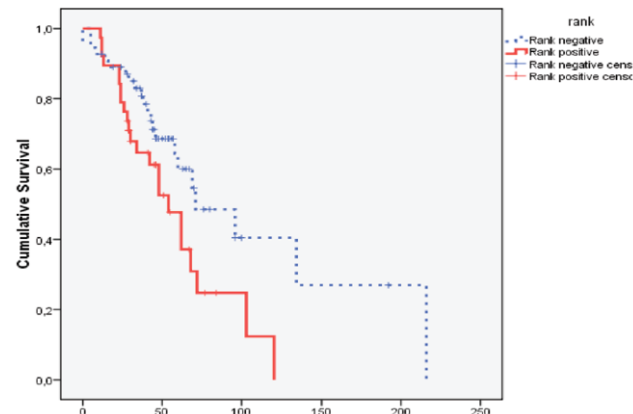
❖ Considering only patients who relapsed to viscera as control group, the RR of bone relapse increased 16.1-fold.

Ibrahim, Clin breast cancer 2011

IRST DATA: The role of gene profiling: tissue and circulating markers in the prediction of bone metastases in breast cancer patients

Marker	Expression in cases	Expression in Controls	Expression in VM	Expression in NEDP
B2m	27	3	0	6
CTGF	30	7	12	3
HPSE	18	3	4	3
SPARC	9	0	0	9
TFF1	63	22	23	21
RANK	18	2	4	0
CXCR4	35	6	13	0
IBSP	20	0	0	0
TFF1/B2m CTGF/RANK	79	28	30	26

Receptor activator of NF- κ B (RANK) expression in primary tumors associates with bone metastasis occurrence in breast cancer patients.

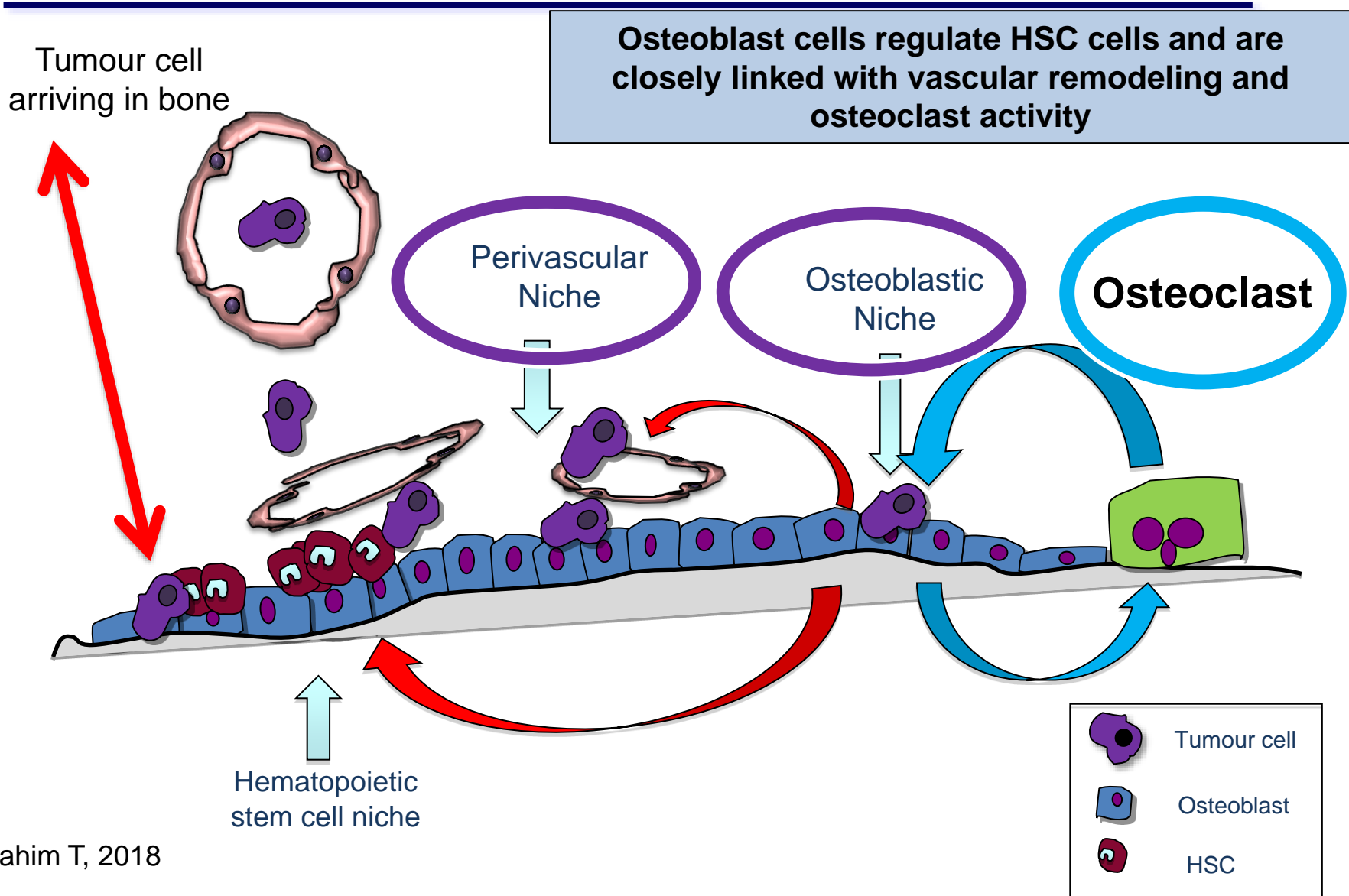


• Immunohistochemical analysis of RANK showed a positive correlation with the development of bone metastases ($P=0.023$)

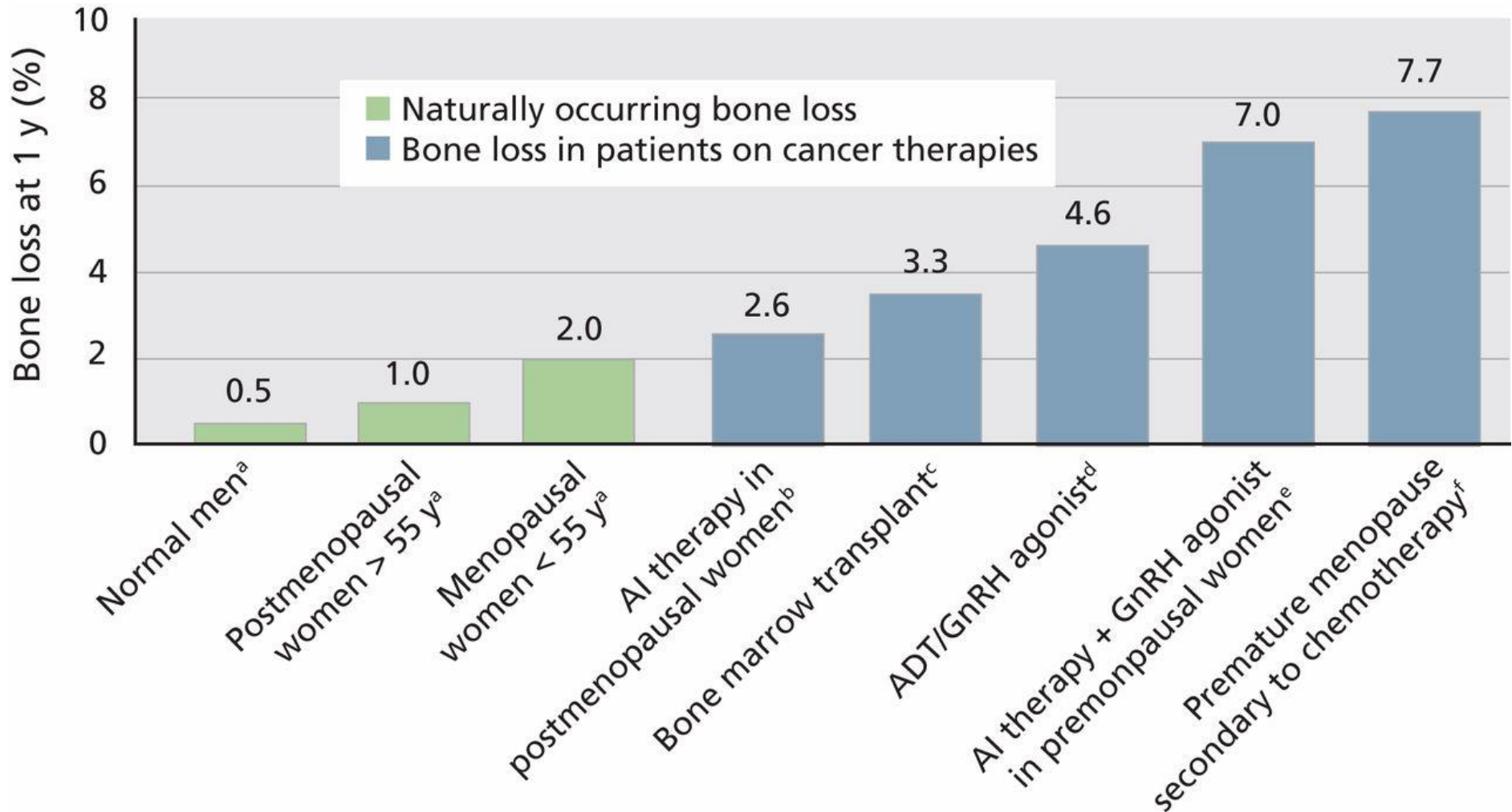
• "RANK-negative" and "RANK-positive" patients had a SDFS of 105.7 months (95% CI: 73.9-124.4) and 58.9 months (95% CI: 34.7-68.5), respectively

Santini D et al PlosOne 2011

The metastatic process/pre-metastatic Niche



BONE LOSS IN PATIENTS ON CANCER THERAPIES



The microenvironment: a role for osteoporosis?

Medical Hypotheses 75 (2010) 514–516



Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy



Osteoporosis as a potential contributor to the bone metastases

Yong-Ping Wu ^{a,1}, Wei-Shan Chen ^{a,2}, Sheng-Jie Xu ^{b,1}, Ning Zhang ^{a,*}

^a Department of Orthopaedics, 2nd Affiliated Hospital, School of Medicine, Zhejiang University, #88 Jiefang Road, Hangzhou 310009, China

^b Institute of Clinical Research, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, #3 East Qingchun Road, Hangzhou 310016, China

Estrogen-deficient osteoporosis enhances the recruitment and activity of osteoclasts by breast cancer cells

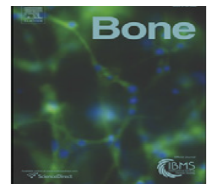
Francesca Salamanna¹, Stefania Pagani^{1,2}, Melania Maglio², Veronica Borsari¹, Gianluca Giavaresi^{1,2}, Alberto M. Martelli³, Francesca Buontempo³ and Milena Fini^{1,2}



Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone



Original Full Length Article

The active role of osteoporosis in the interaction between osteoblasts and bone metastases

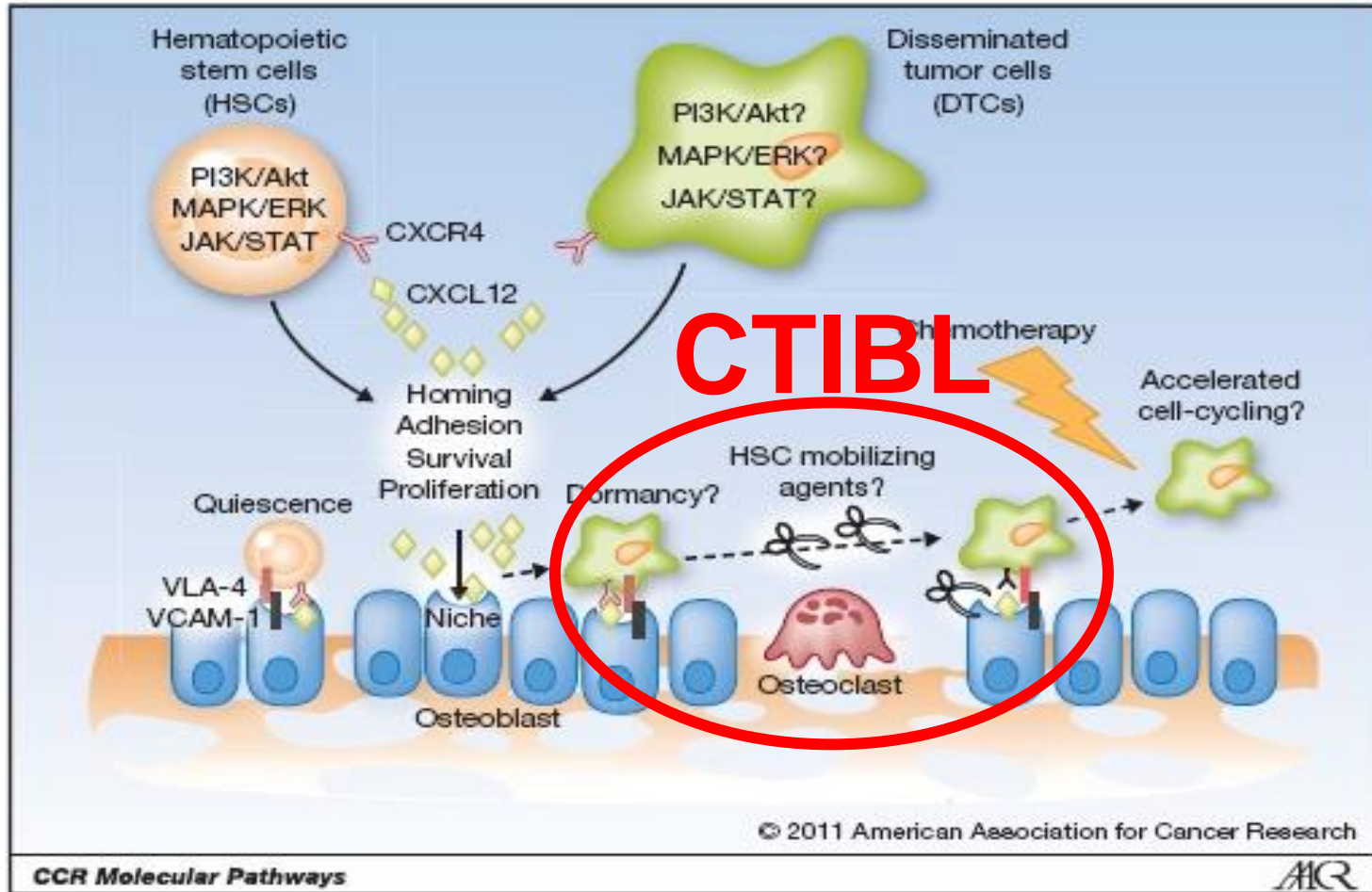
Stefania Pagani ^{a,b,*}, Milena Fini ^{a,b}, Gianluca Giavaresi ^{a,b}, Francesca Salamanna ^b, Veronica Borsari ^b

^a Laboratory of Preclinical and Surgical Studies, Rizzoli Orthopaedic Institute, Bologna, Italy

^b Laboratory of Biocompatibility, Technological Innovations and Advanced Therapies, Department RIT Rizzoli, Rizzoli Orthopaedic Institute, Bologna, Italy



Bone Microenvironment



Bone Targeted Therapy (Bone modifying agents)

Advanced setting



Adjuvant setting

Evolving cancer–niche interactions and therapeutic targets during bone metastasis

Reviews Nature 2021

Robert L. Satcher¹ and Xiang H.-F. Zhang^{2,3,4}

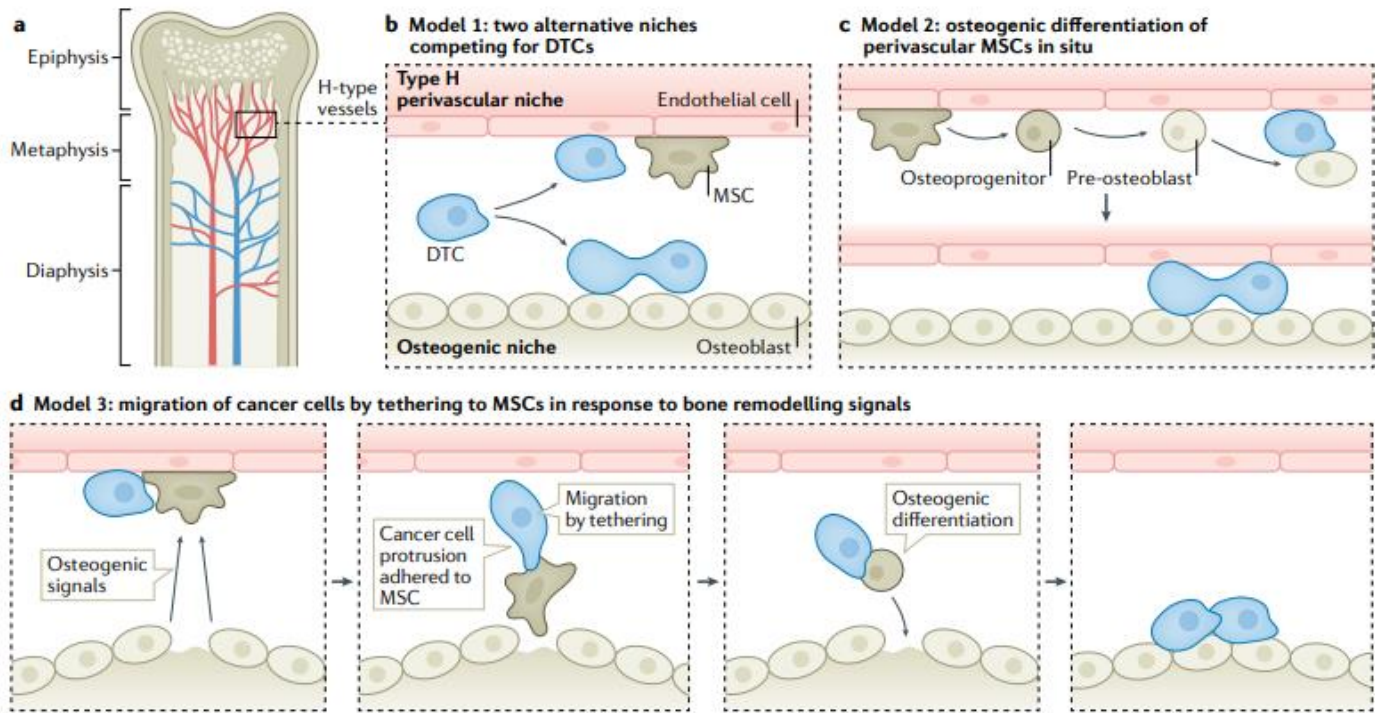
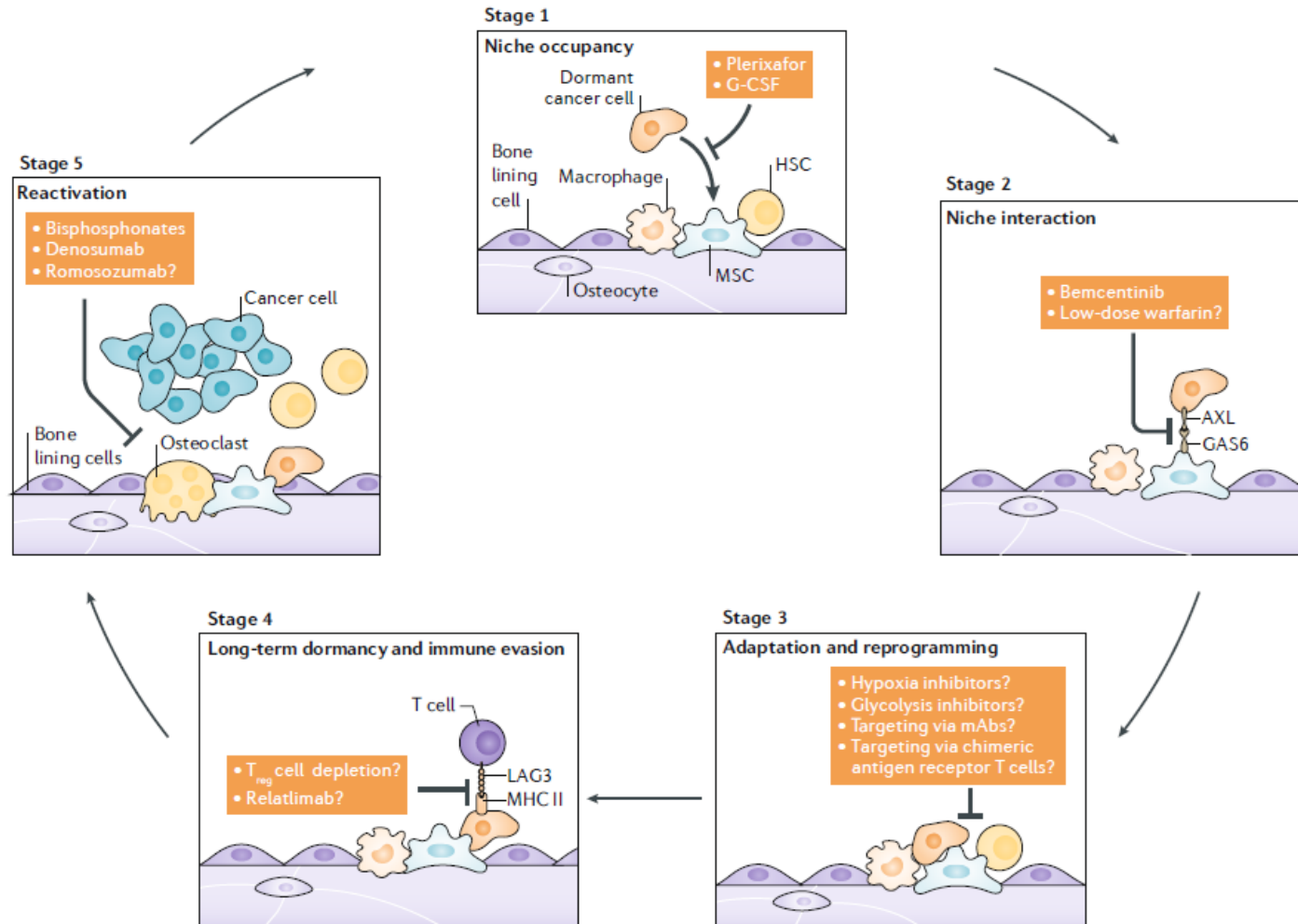


Fig. 2 | The possible relationship between different microenvironment niches during early-stage bone metastasis. **a** | The vascular network in the bone marrow is in close proximity to trabecular bones and endosteum, where osteogenic cells localize. The perivascular niche and osteogenic niche may have a few possible relationships during bone metastasis. **b** | Model 1: the two niches may compete for disseminated tumour cells (DTCs). DTCs localize to the perivascular niche and osteogenic niche, after which they may enter dormancy or begin proliferation, respectively. **c** | Model 2: the perivascular mesenchymal cells of type H vessels possess mesenchymal stem cell (MSC) activities and may differentiate

into osteogenic cells. Therefore, in situ differentiation may create a new osteogenic niche adjacent to the perivascular niche, and may terminate dormancy and trigger proliferation of cancer cells. **d** | Model 3: dormant DTCs and quiescent MSCs colocalize in the perivascular niche. Bone homeostasis or pathological bone injuries release osteogenic signals to mobilize MSCs. Cancer cells may form specialized protrusions to attach to MSCs that are undergoing chemotaxis towards the source of osteogenic signals. Upon arrival, the MSCs differentiate into osteoblasts. The associated cancer cells remain in the newly formed osteogenic niche and begin proliferation.

Niche-targeted therapies to prevent bone metastasis



Evolving cancer–niche interactions and therapeutic targets during bone metastasis

Reviews Nature 2021

Robert L. Satcher¹ and Xiang H.-F. Zhang^{2,3,4}

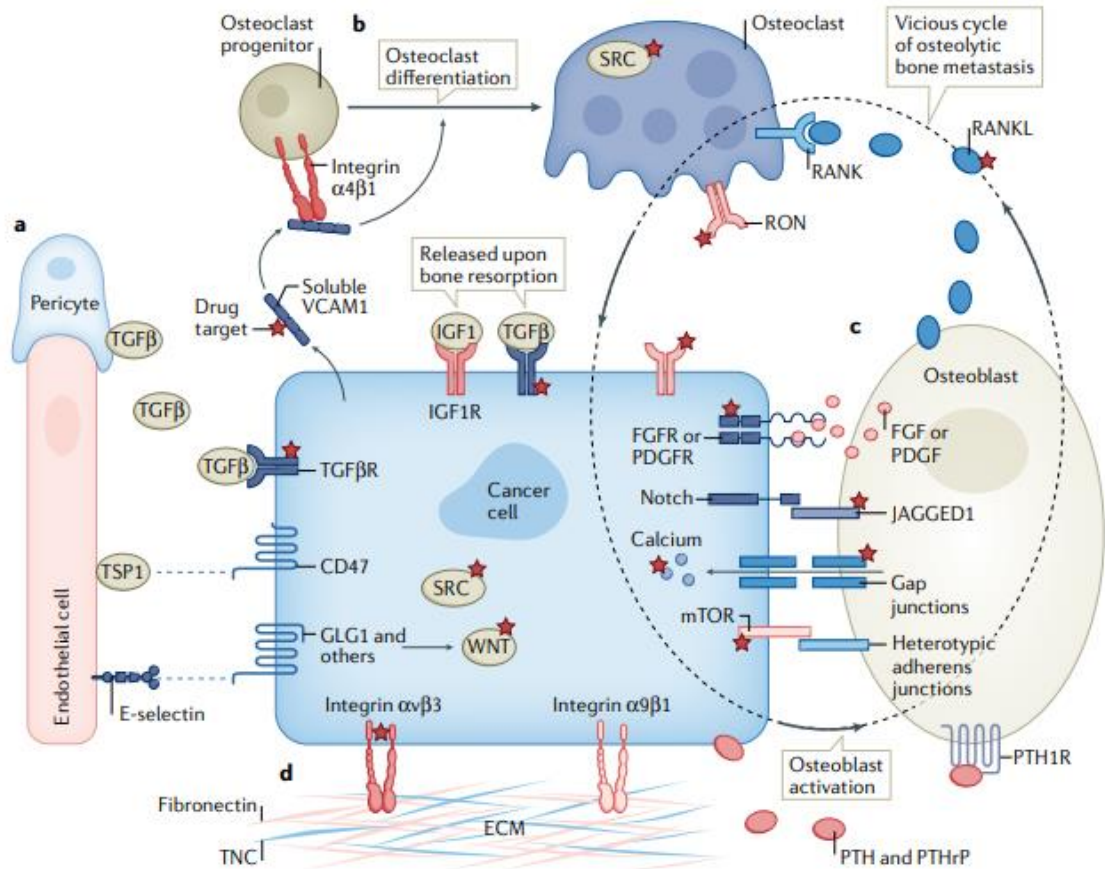
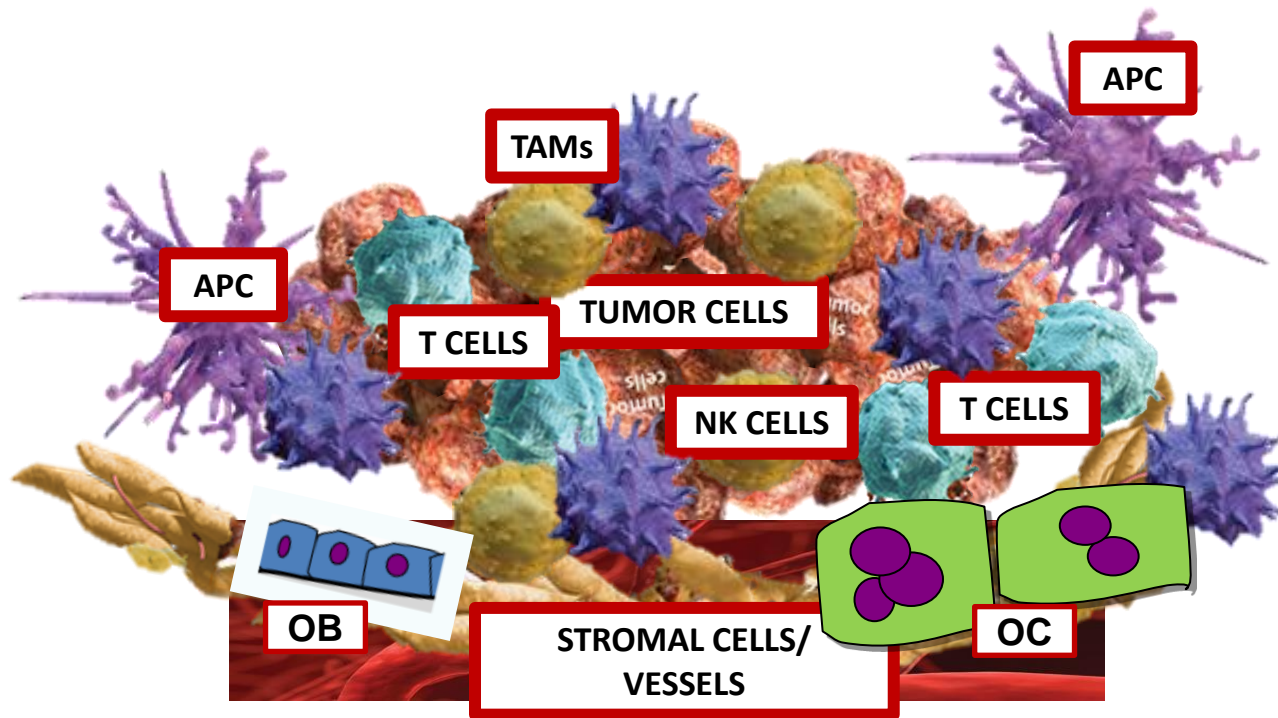


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Cancer and Tumor Microenvironment



OPEN

First prospective data on breast cancer patients from the multicentre italian bone metastasis database

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ORIGINAL RESEARCH
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Prospective data from
the Italian Bone
Metastases Data Base

Immune Checkpoint Inhibitors With or Without Bone-Targeted Therapy in NSCLC Patients With Bone Metastases and Prognostic Significance of Neutrophil-to-Lymphocyte Ratio

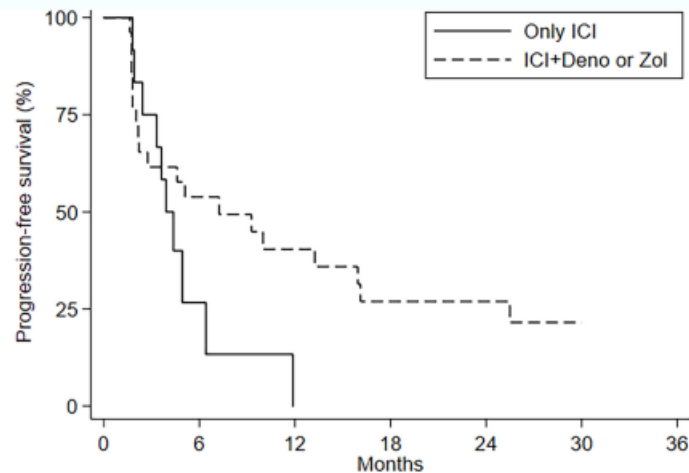
Alberto Bongiovanni^{1*}, Flavia Foca², Jessica Menis^{3,4,5}, Stefania Luigia Stucci⁶, Fabrizio Artioli⁷, Valentina Guadalupi⁸, Maria Rosachiara Forcignanò⁹, Manuela Fantini¹⁰, Federica Recine¹¹, Laura Mercatali¹, Chiara Spadazzi¹, Marco Angelo Burgio¹², Valentina Fausti¹, Anna Miserocchi² and Toni Ibrahim¹

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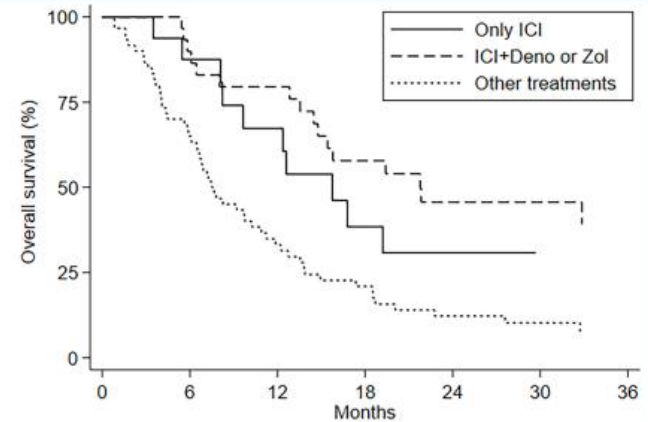
Immune Checkpoint Inhibitors With or Without Bone-Targeted Therapy in NSCLC Patients With Bone Metastases and Prognostic Significance of Neutrophil-to-Lymphocyte Ratio

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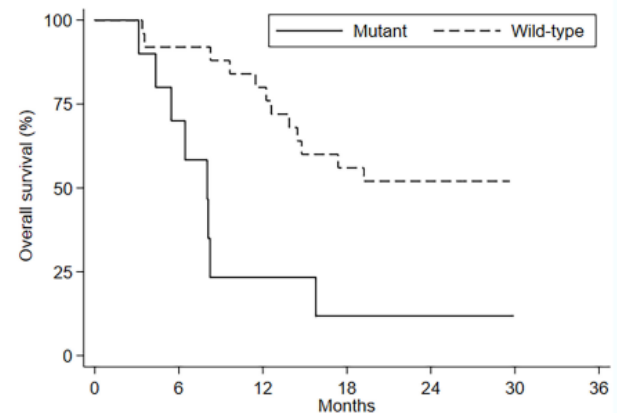
OPEN ACCESS



Number at risk							
Only ICI	16	2	0	0	0	0	0
ICI+Deno or Zol	30	13	9	6	5	4	3

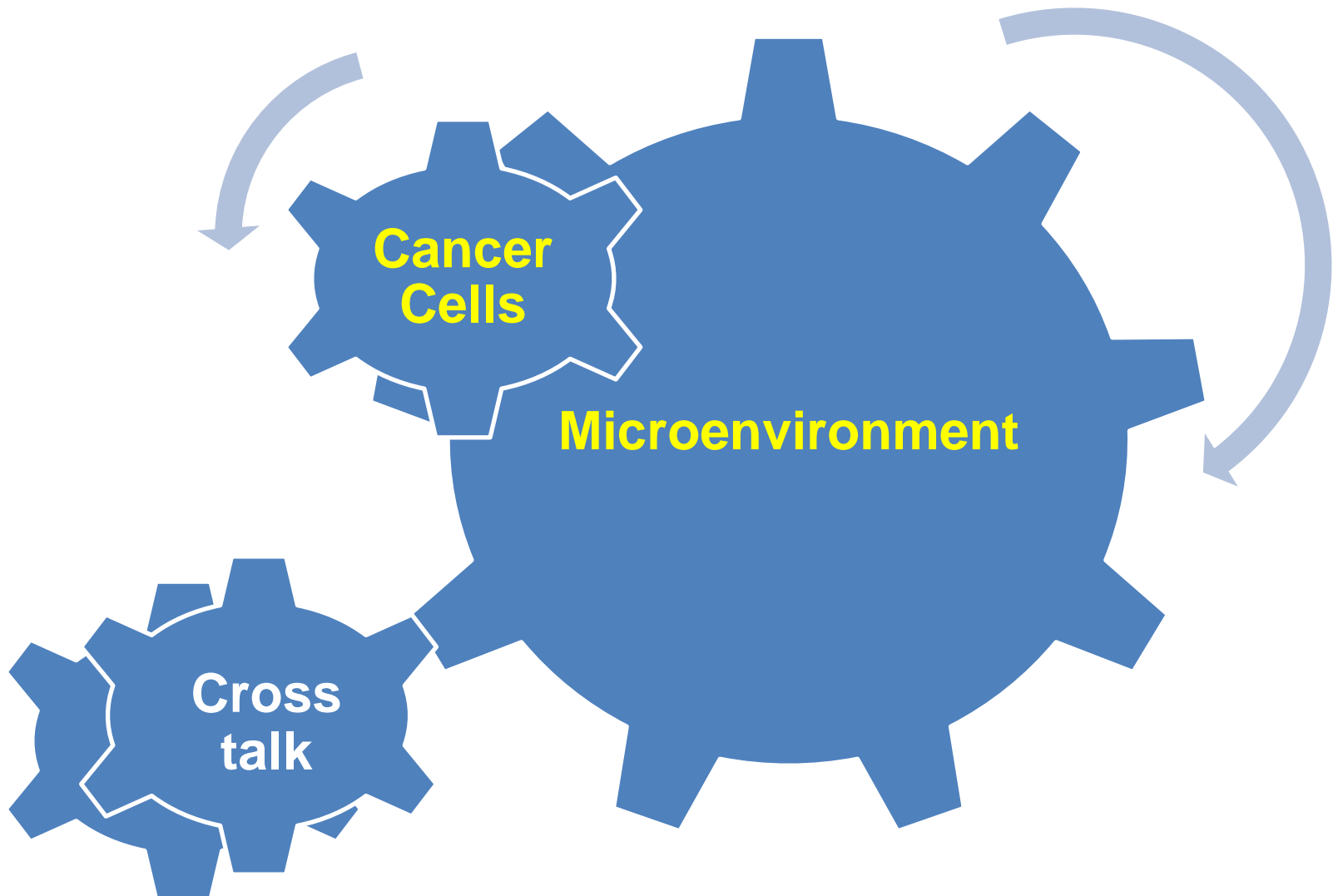


Number at risk							
Only ICI	16	14	10	5	4	3	3
ICI+Deno or Zol	30	26	22	15	10	8	6
Other treatments	60	39	19	12	7	4	3



Number at risk							
Mutant	10	6	2	1	1	1	1
Wild-type	25	23	20	14	11	7	7

Hot topic in Oncology





L'Oncologia moderna 2022

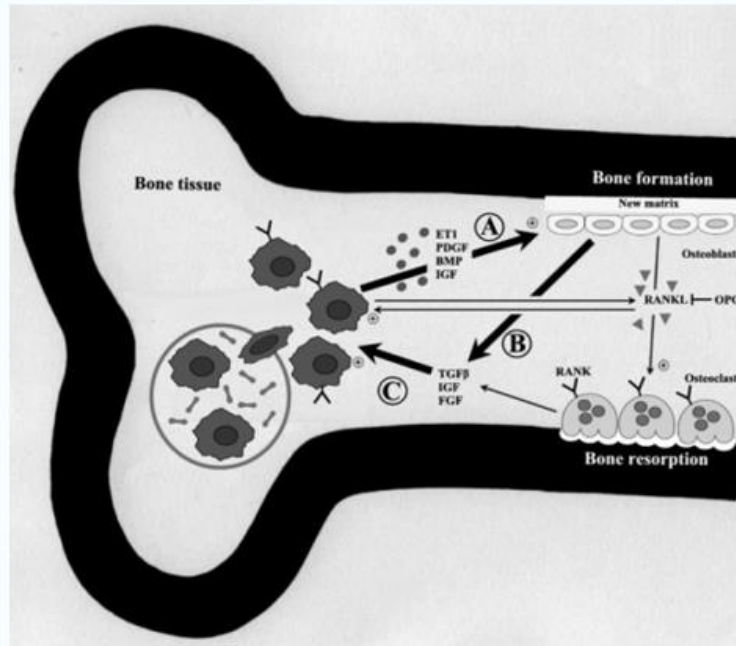
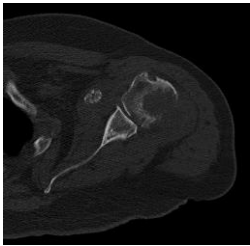
PRECISION
Targeted Therapies
Based on
Molecular Diagnostics

PERSONALIZED
Prevention and Treatment based
on Environment, Lifestyle,
and Genes

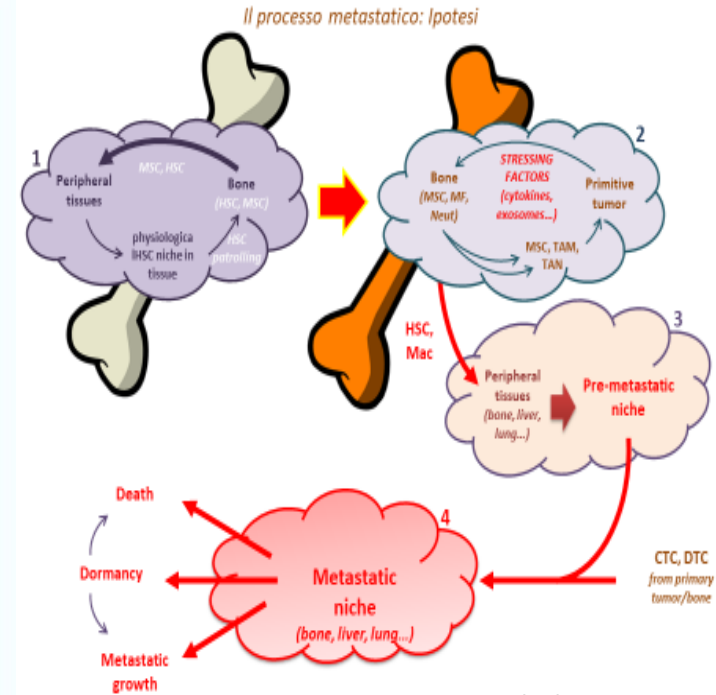
Precision Medicine
is science – a new wave of
evidence-based medicine

Personalized Medicine
is a practice – managing a
patient's care more
holistically

The Osteoncology



Ibrahim T, Cancer 2010



Ibrahim T, 2018

2000

Clinical
needs M1

2010

Physiopathological
needs

2022

Clinical
needs M0/M1

2000

Professional needs

2022

**Vision of
Prof. Amadori**

**Clinical and Lab
Researchers**

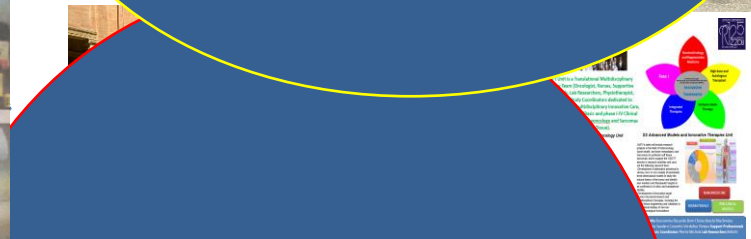
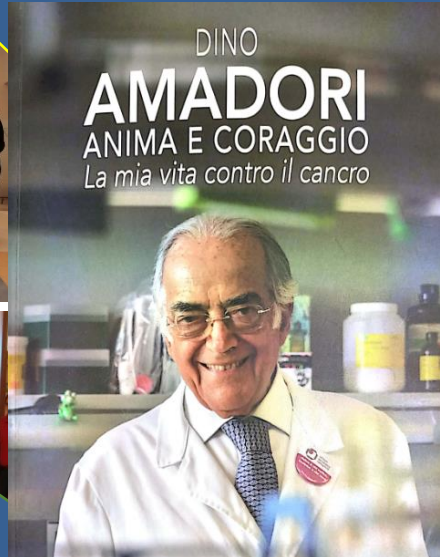
Networks

**Dialogue
=
Cross Talk**

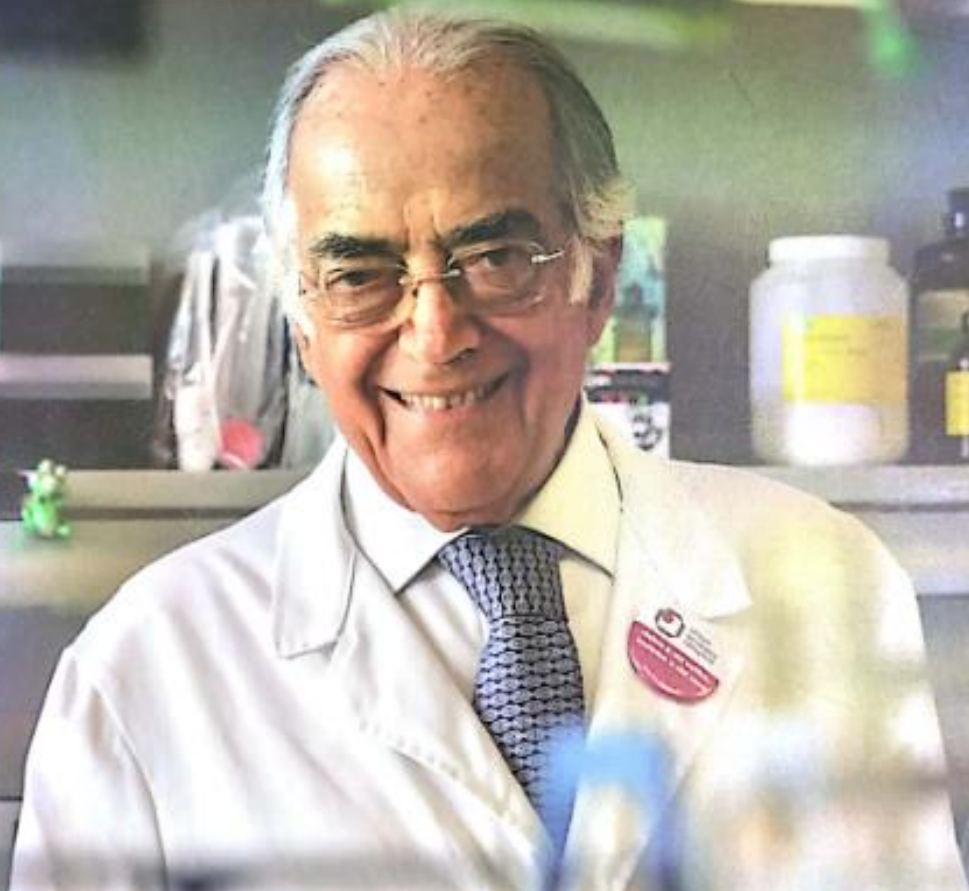
Volunteer Associations

**Multi/
Interdisciplinarity**

Patients



DINO
AMADORI
ANIMA E CORAGGIO
La mia vita contro il cancro



Meldole 14.05.2018

DINO
AMADORI
ANIMA E CORAGGIO
La mia vita contro il cancro

mi', se quando
una telefonata da
venuele, tanta
stata fatta e
giorno e notte.
Laboratori -
me e amate
Ben Amadori

