

**SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA**
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori
Istituto di Ricovero e Cura a Carattere Scientifico



**ISTITUTO
SCIENTIFICO
ROMAGNOL
PER LO STUDIO E LA CURA
DEI TUMORI**

**VI CONGRESSO NAZIONALE DELLA SOCIETÀ ITALIANA
DI OSTEONCOLOGIA (ISO)**
Padova, 14-15 Novembre 2017
PALAZZO ZACCO

Presidenti: D. Santini, V. Zagonel
Comitato Scientifico ISO: A. Berruti, F. Bertoldo, N. Calipari, R. Casadei, T. Ibrahim, G. Lanzetta
Responsabili Scientifici: A. Brunello, S. Zovato

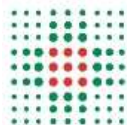
Con il patrocinio di:

Associazione Italiana di Oncologia Medica  Istituto Oncologico Veneto  Rete Oncologica Veneta 

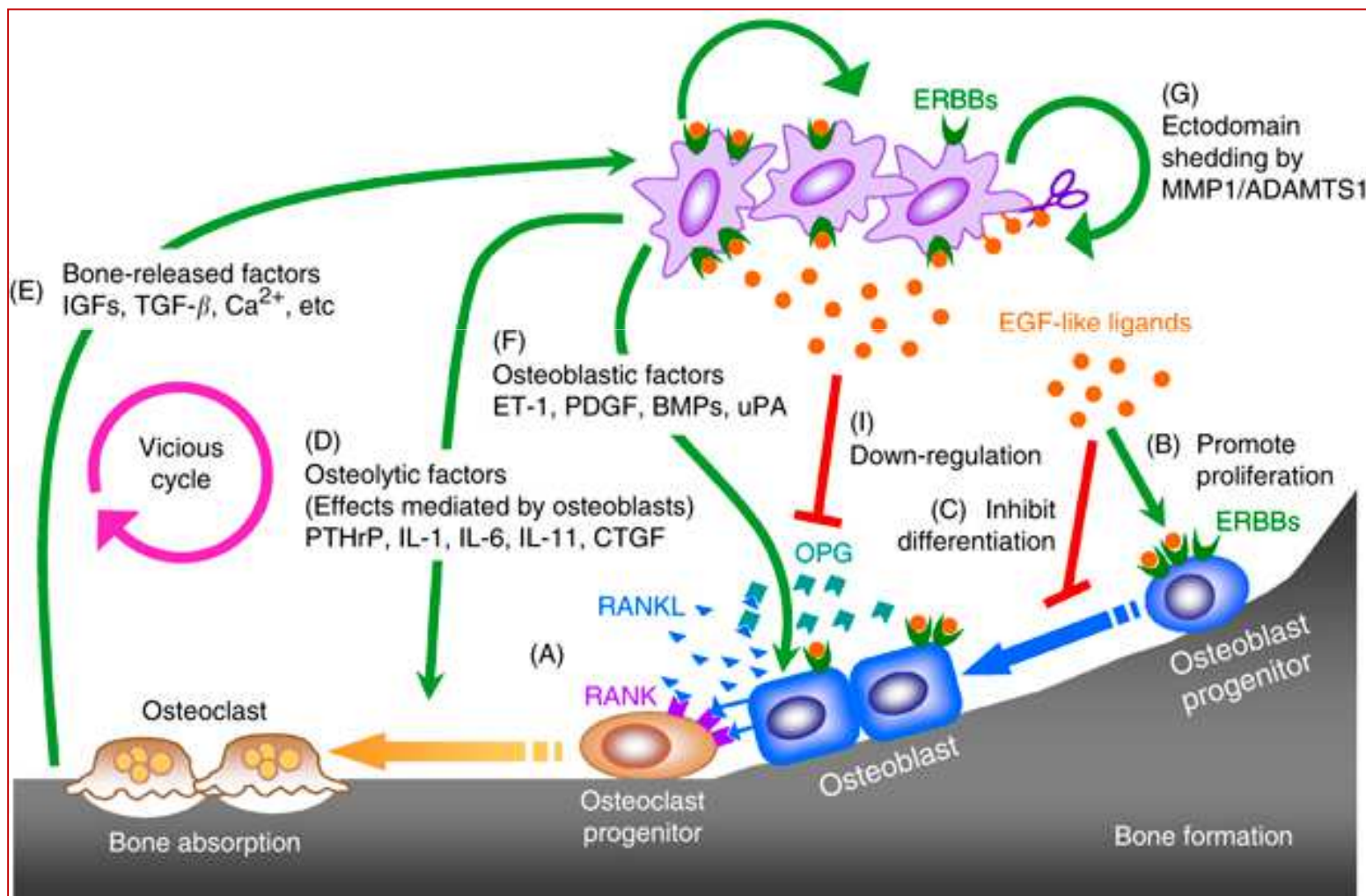
Bone targeted therapy and TOR inhibitor

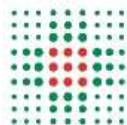
**Laura Mercatali
CDO-TR**

**IRCCS IRST
Meldola**

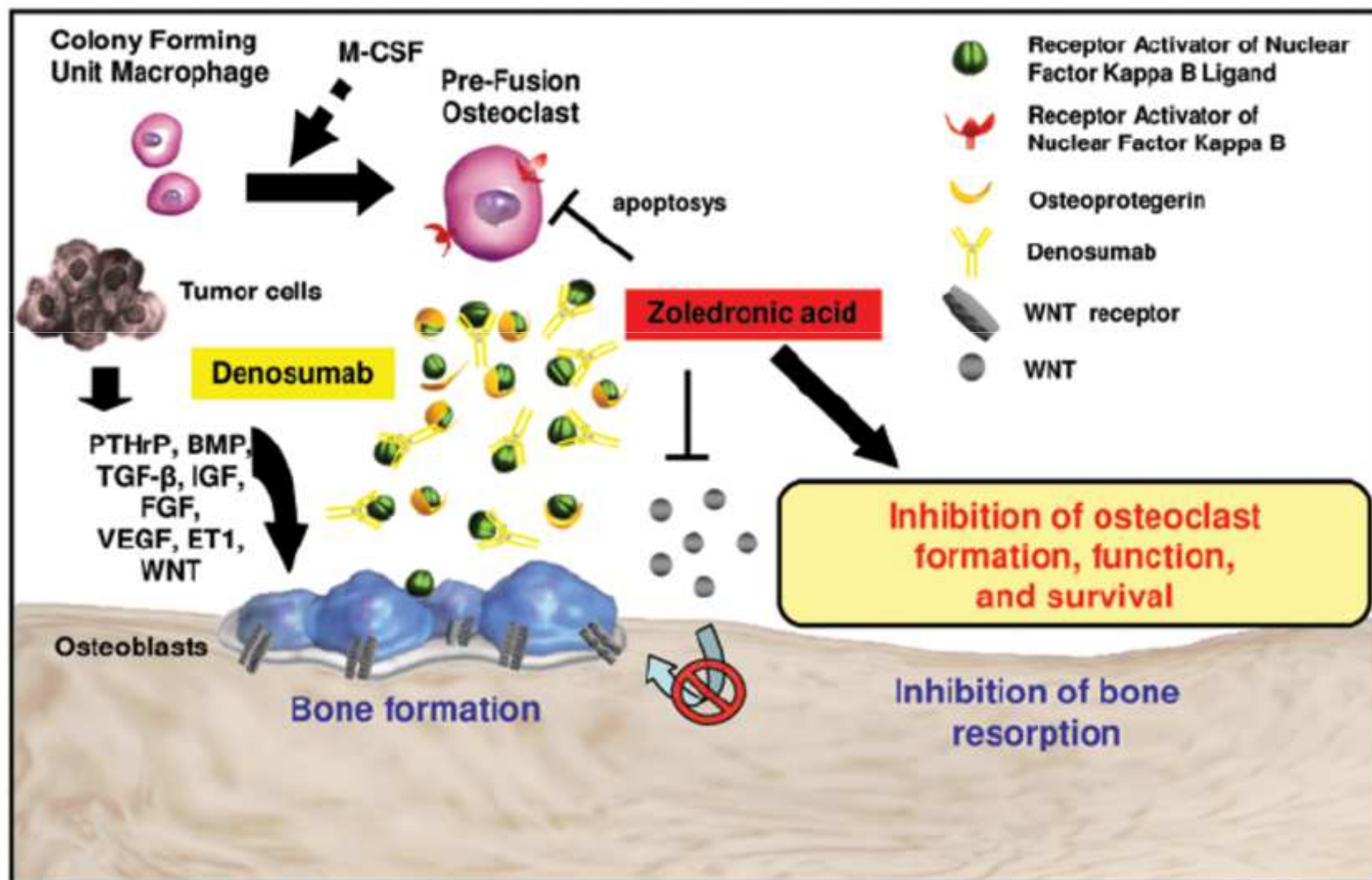


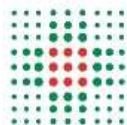
Vicious cycle of bone metastases



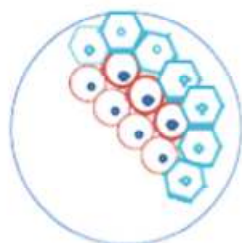


Rationale for the use of BTT

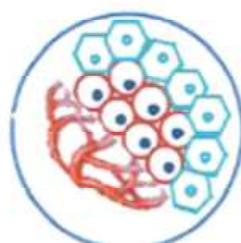




Antitumoral effect of Zol



Tumour cells



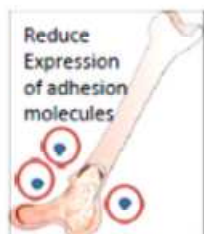
Inhibition of
angiogenesis



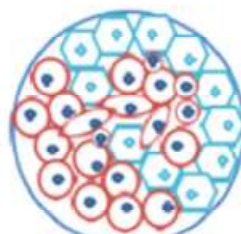
Inhibition of tumour
cell proliferation
and induction of
apoptosis



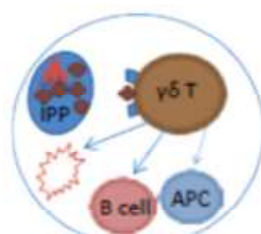
Augmentation of inhibitory
effect of cytotoxic agents



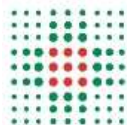
Decrease tumour
cells adhesion to bone



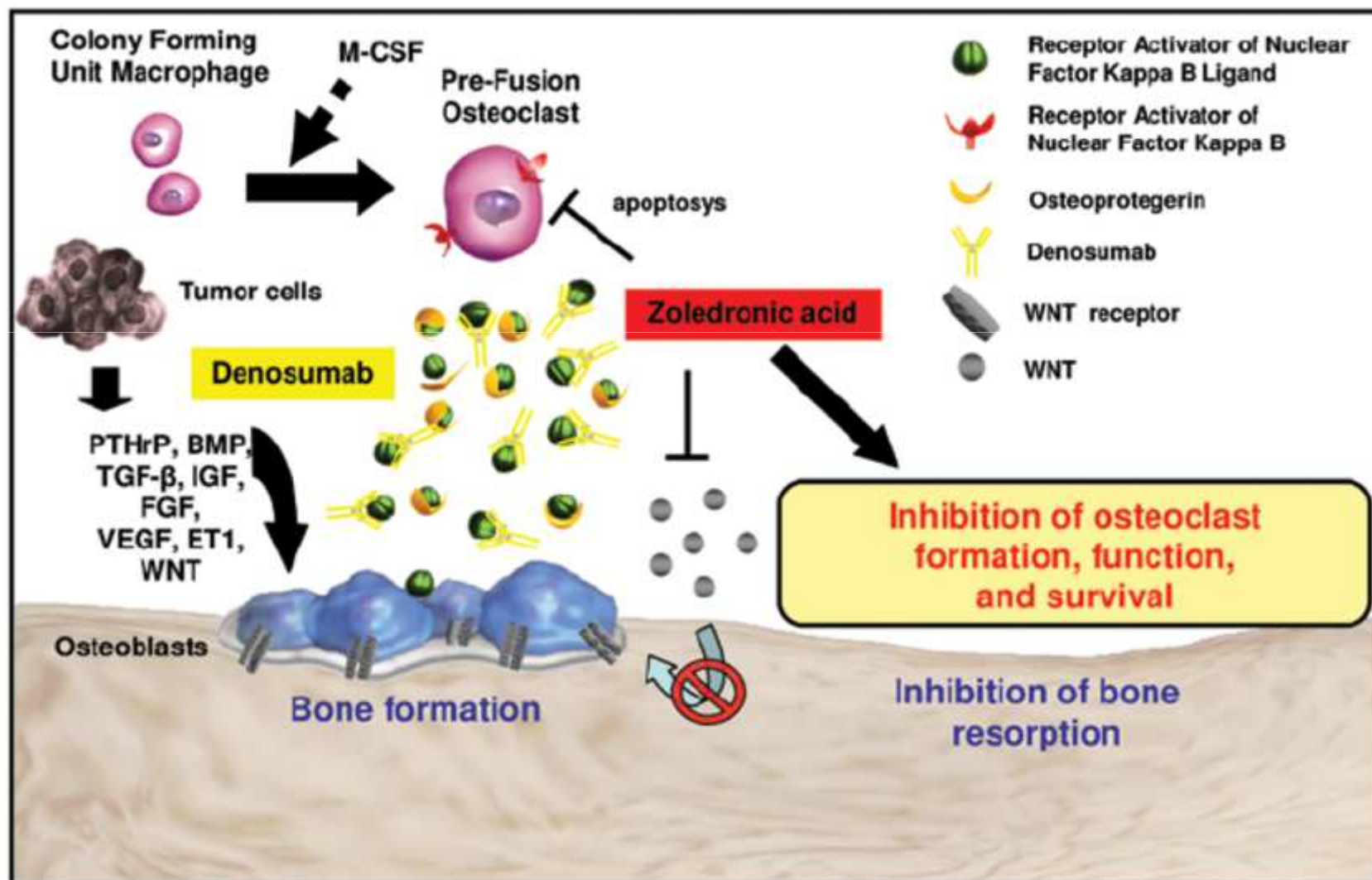
Decrease in tumour cells
invasion and migration
and disorganization of cell
cytoskeleton

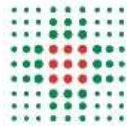


Activation of $\gamma\delta$ T cells

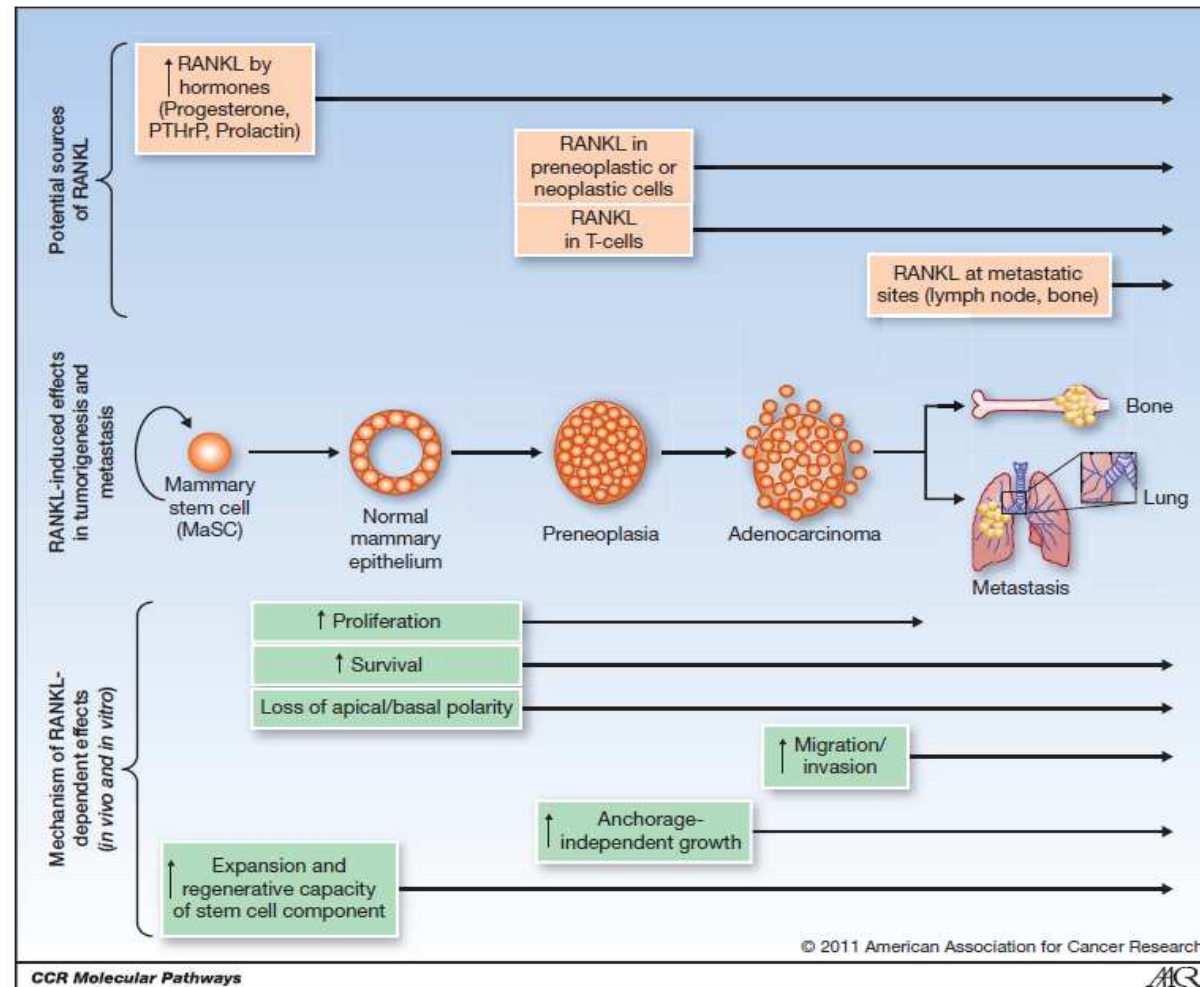


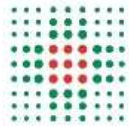
Rationale for the use of BTT



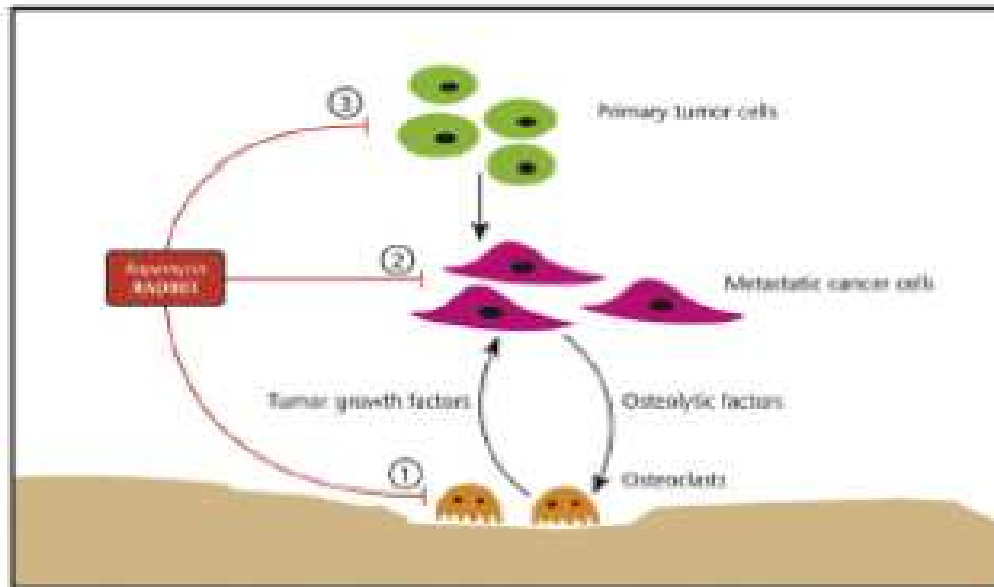


Direct protumorigenic and prometastatic activities of RANK



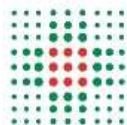


Rationale for the use of mTOR inhibitor



clinical trial BOLERO-2 :eve+exe reduced the incidence of bone progression in the overall population.

The PFS in bone also was significantly higher in the subset of patients with bone metastases at baseline treated with the combination therapy compared to controls



Preclinical pharmacology: From cancer cell side

Ibrahim et al. *Cancer Cell International* 2012, 12:48
<http://www.cancerci.com/content/12/1/48>



PRIMARY RESEARCH

Open Access

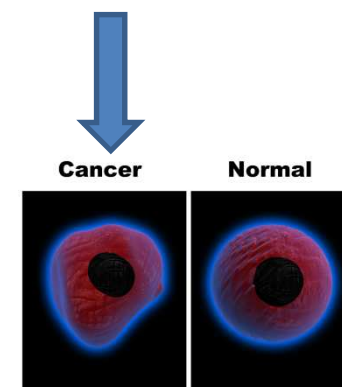
Inhibition of breast cancer cell proliferation in repeated and non-repeated treatment with zoledronic acid

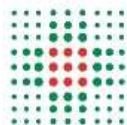
Toni Ibrahim^{1*}, Laura Mercatali^{1*}, Emanuele Sacanna¹, Anna Tesei², Silvia Carloni², Paola Ulivi², Chiara Liverani¹, Francesco Fabbri², Michele Zanoni¹, Wainer Zoli² and Dino Amadori¹

INTERNATIONAL JOURNAL OF ONCOLOGY 42: 1263-1270, 2013

Cisplatin in combination with zoledronic acid: A synergistic effect in triple-negative breast cancer cell lines

TONI IBRAHIM^{1*}, CHIARA LIVERANI^{1*}, LAURA MERCATALI¹, EMANUELE SACANNA¹,
MICHELE ZANONI¹, FRANCESCO FABBRI², WAINER ZOLI² and DINO AMADORI¹





Preclinical pharmacology: From healthy cell side

Bone 66 (2014) 214–222



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



Original Full Length Article

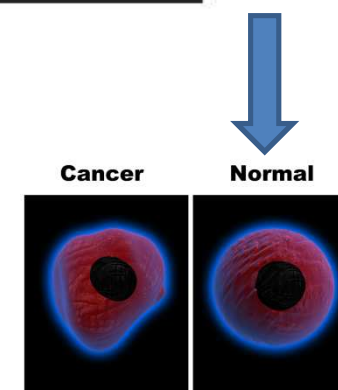
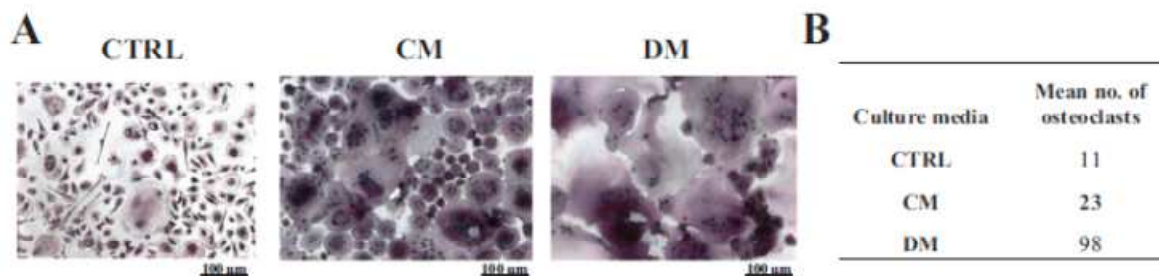
CSF-1 blockade impairs breast cancer osteoclastogenic potential in co-culture systems

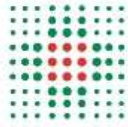


Chiara Liverani ^{a,*}, Laura Mercatali ^a, Chiara Spadazzi ^a, Federico La Manna ^a, Alessandro De Vita ^a, Nada Riva ^a, Sebastiano Calpona ^a, Marianna Ricci ^a, Alberto Bongiovanni ^a, Erica Gunelli ^a, Michele Zanoni ^b, Francesco Fabbri ^b, Wainer Zoli ^b, Dino Amadori ^a, Toni Ibrahim ^a

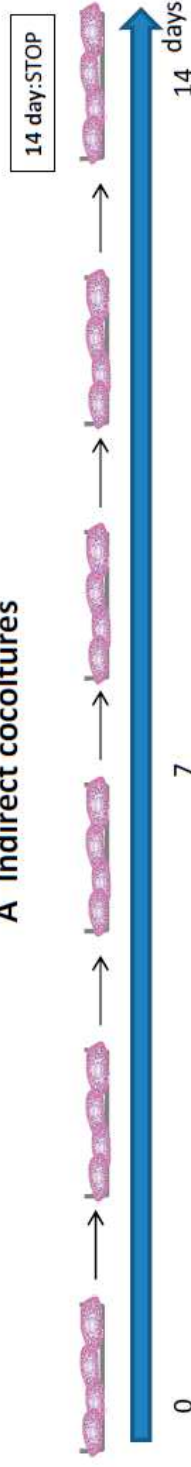
^a Osteoncolology and Rare Tumors Center, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via Piero Maroncelli 40, 47014 Meldola, FC, Italy

^b Biosciences Laboratory, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Via Piero Maroncelli 40, 47014 Meldola, FC, Italy





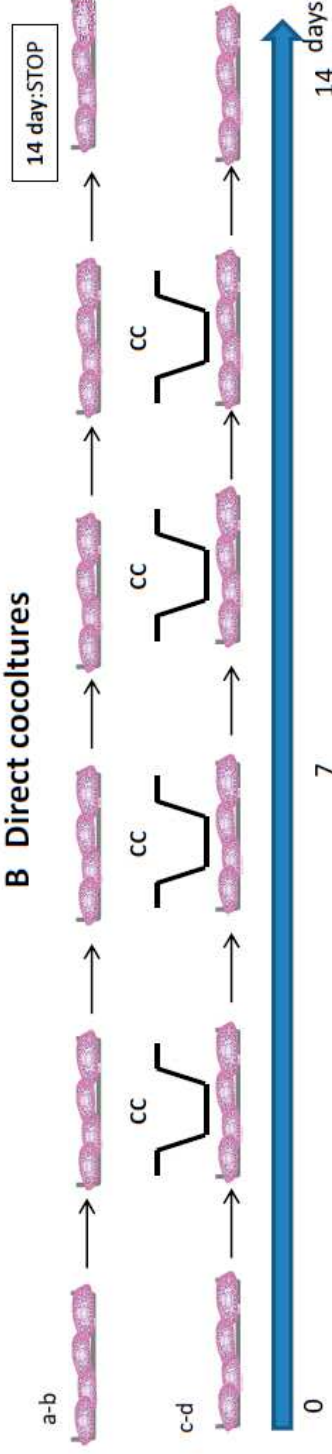
A Indirect cocultures



Tested conditions:

CTRL-: Negative control, PBMCs are cultured in presence of complete α MEM medium
CTRL+: Positive control, PBMCs are cultured in presence of complete α MEM medium supplied with MCSF and RANKL
CM: PBMCs are cultured for the entire experiments with conditioned medium (CM) and without growth factors

B Direct cocultures



Tested conditions:

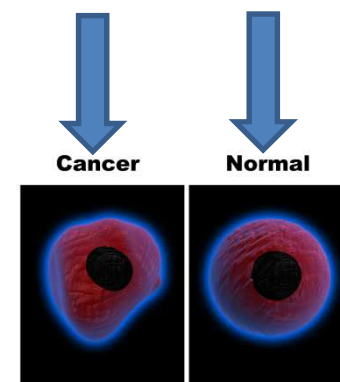
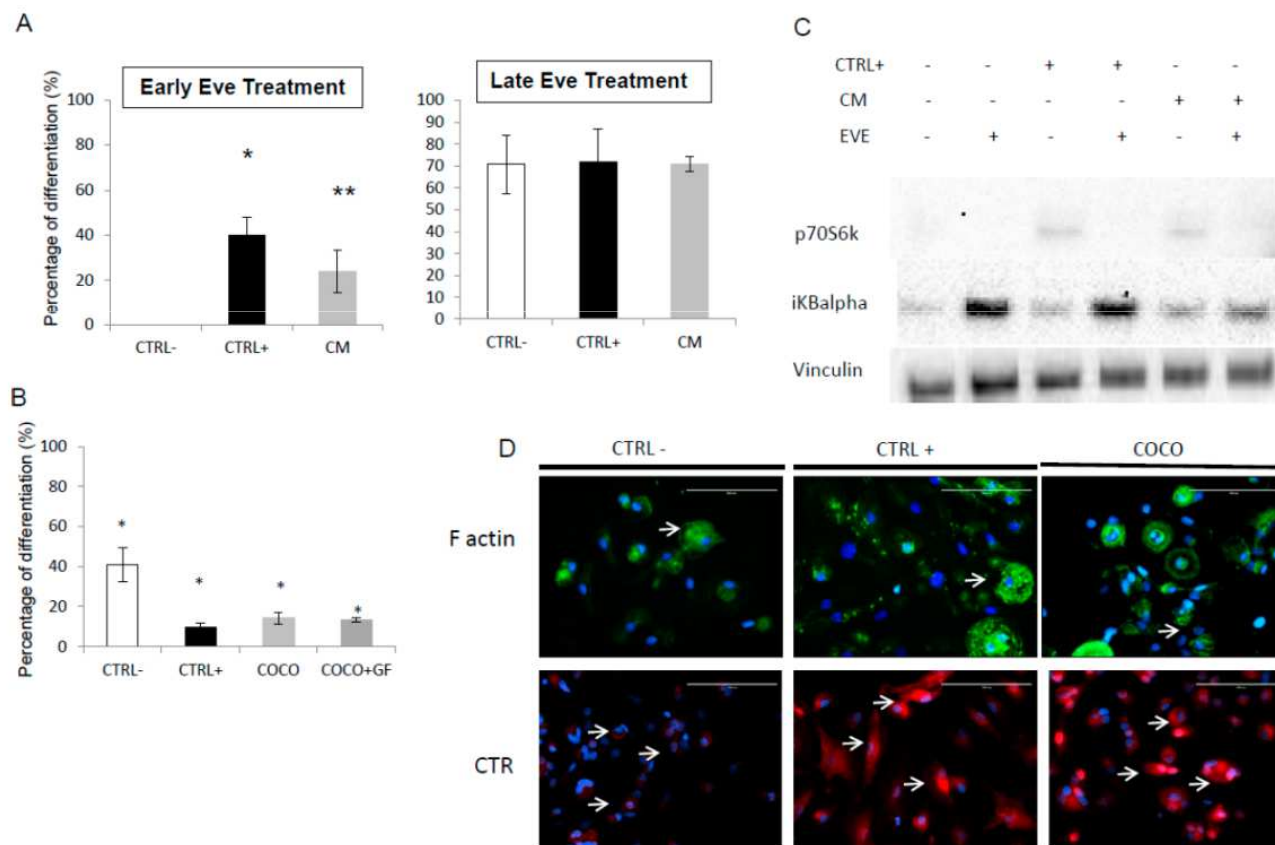
CTRL-: negative control (a)
CTRL+: positive control (b)
COCO: PBMCs are cultured from day 3 to day 11 with sharing of medium with cancer cells seeded in transwell and inserted over the monocytes (c)
COCO+GF*: PBMCs are cultured as condition C with medium supplies of growth factor MCSF and RANKL (d)



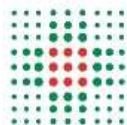
Article

The Effect of Everolimus in an In Vitro Model of Triple Negative Breast Cancer and Osteoclasts

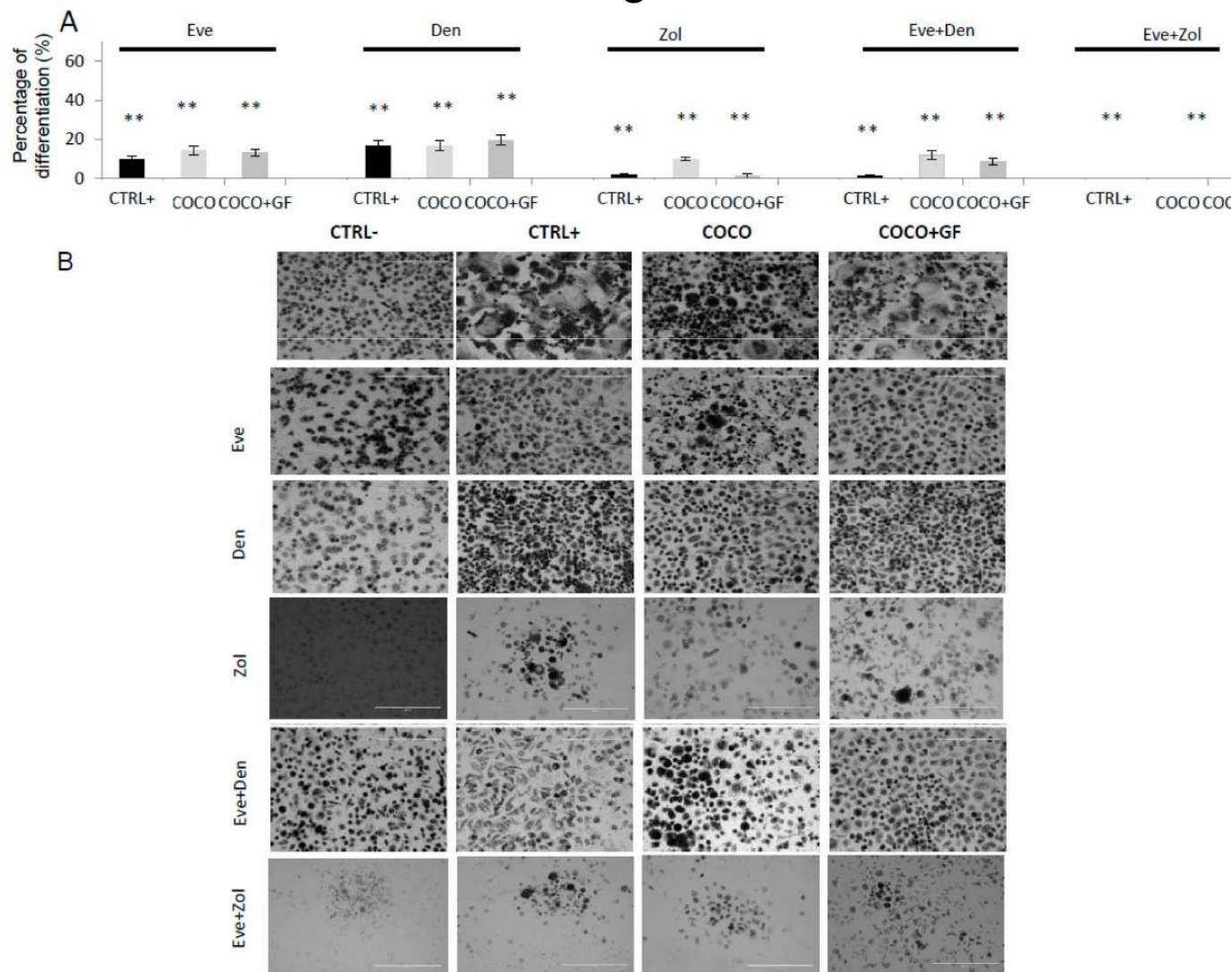
Laura Mercatali ^{*,†}, Chiara Spadazzi [†], Giacomo Misericocchi, Chiara Liverani, Alessandro De Vita, Alberto Bongiovanni, Federica Recine, Dino Amadori and Toni Ibrahim

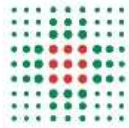


Everolimus inhibits osteoclastogenesis in a coculture model of breast cancer and osteoclasts



The combination of everolimus and zoledronic acid completely abrogated osteocalcogenesis



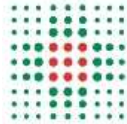


Take home message

- Eve is an effective strategy to break the vicious cycle of bone metastasis.
- we observed a higher responsiveness to Zol of the bone metastasis model induced by triple negative BC cells.
- We report here a biologic rationale for the treatment of triple negative BC

Preclinic can give the rationale to test a drug in different setting respect to guide line indication





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RESEARCH ARTICLE

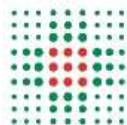
Open Access

Concurrent antitumor and bone-protective effects of everolimus in osteotropic breast cancer

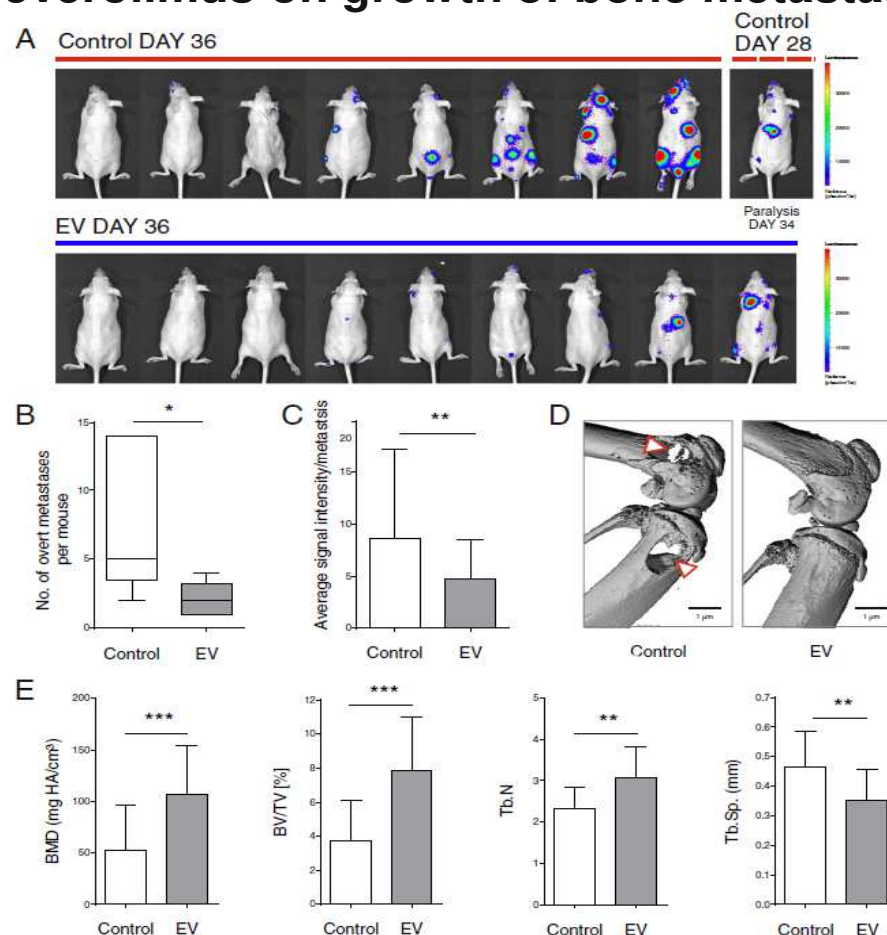


Andrew J. Browne^{1,2*}, Marie L. Kubacki^{1,2*}, Andy Göbel^{1,2}, Feyman Hirdji³, David Chen⁴, Martina Ranner^{1,2}, Friedrich Stöckel⁵, Lorenz C. Hofbauer^{1,2*} and Tilman D. Sacher^{1,2*}

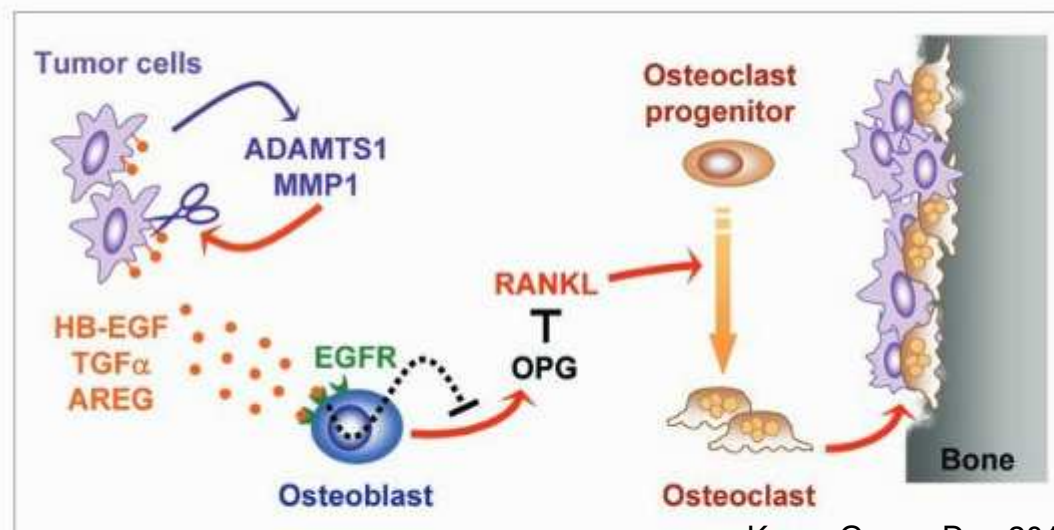
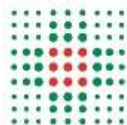
Breast Cancer Research 2017



Effects of everolimus on growth of bone metastases



Everolimus inhibited the metastatic growth of MDA-MB-231 cells by 70 while preserving bone mass in an intracardiac model of bone metastasis.




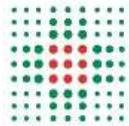
Kang, Genes Dev 2011



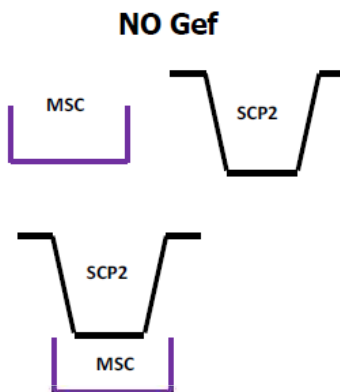
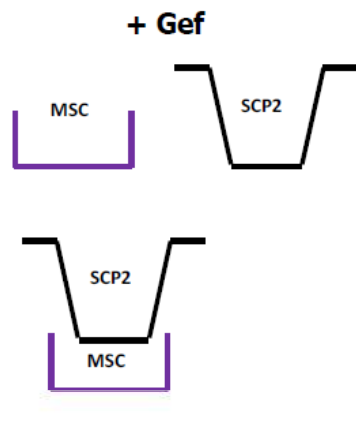
Article

Tumor-Stroma Crosstalk in Bone Tissue: The Osteoclastogenic Potential of a Breast Cancer Cell Line in a Co-Culture System and the Role of EGFR Inhibition

Laura Mercatali ^{1,*}, Federico La Manna ¹, Giacomo Miserocchi ¹, Chiara Liverani ¹,
Alessandro De Vita ¹ , Chiara Spadazzi ¹, Alberto Bongiovanni ¹, Federica Recine ¹,
Dino Amadori ¹, Martina Ghetti ^{1,2} and Toni Ibrahim ¹



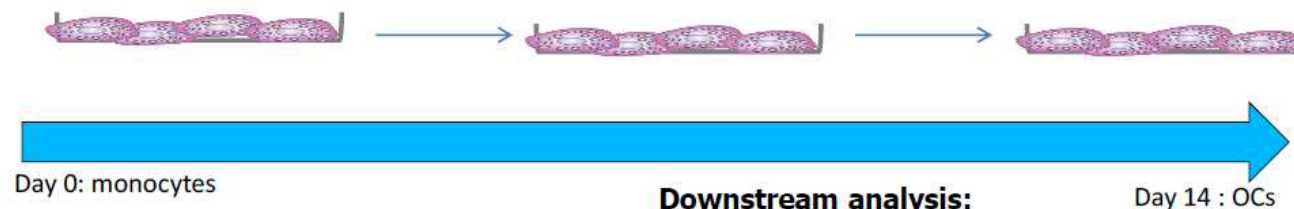
Study design:



Analyses to do:

- MSC: Evaluation of EGFR-P to ascertain inhibition of EGFR
- SCP2: Gene expression analyses to evaluate the effect of the interaction with MSC on tumor cells.

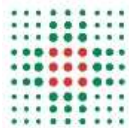
We conditioned monocytes with the CM collected from all the treated/untreated conditions



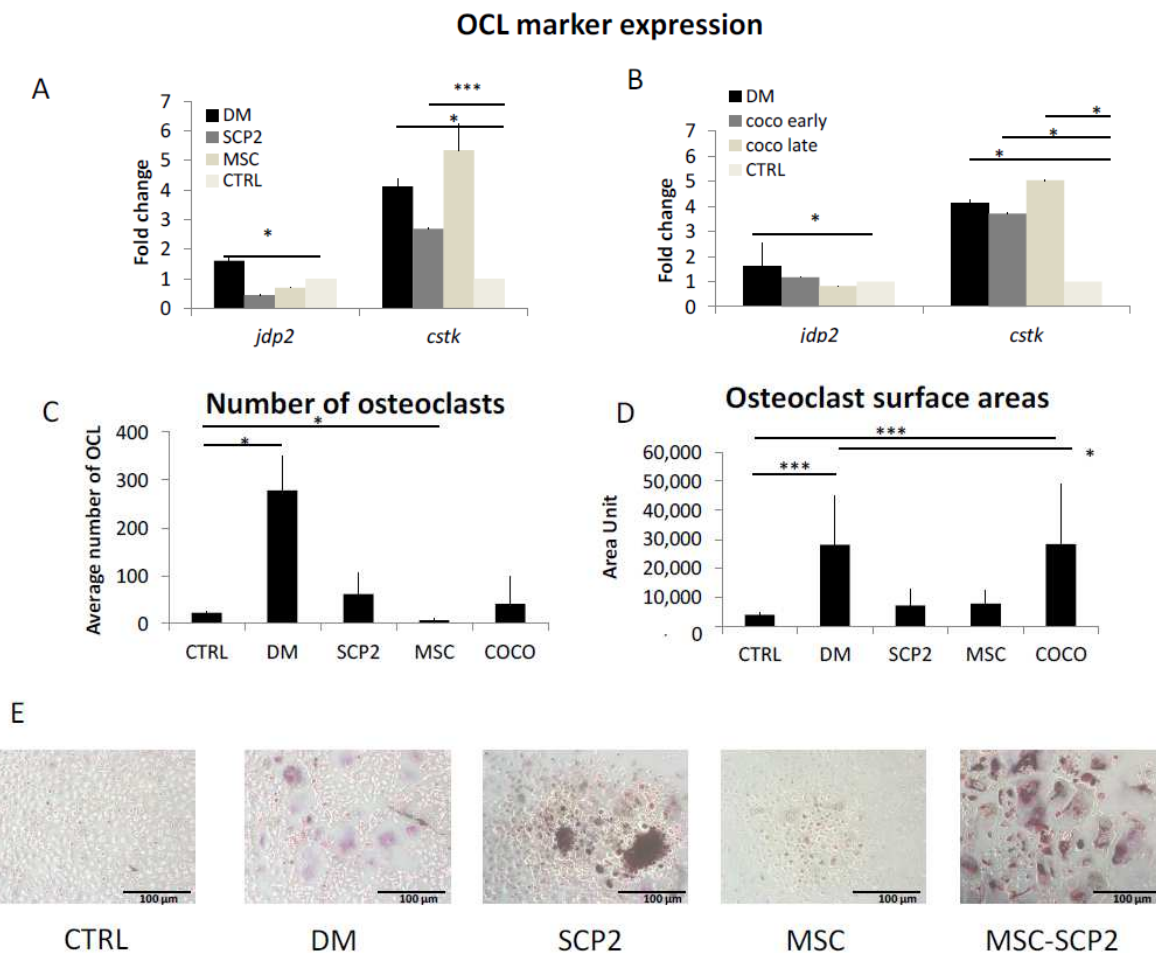
RNA → Osteoclastogenesis markers

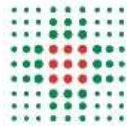
TRAP → osteoclast count

Model improvement: MSC effect
Combination of gefitinib with BTT and eve

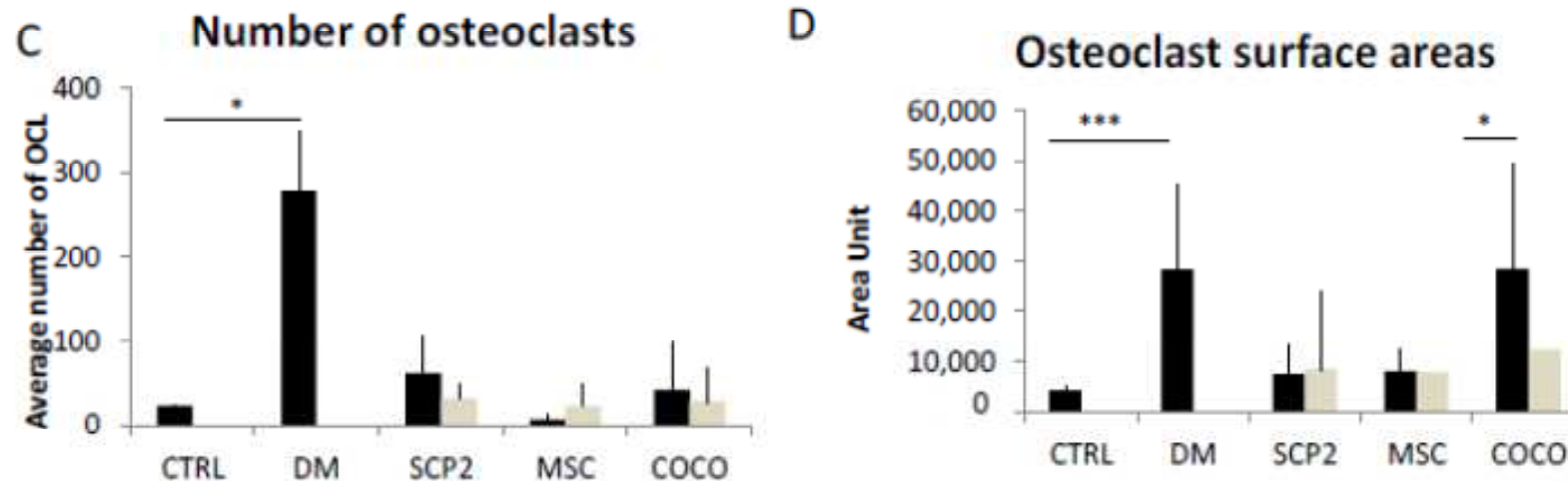


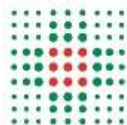
SCP2 and MSC mono-cultures and COCO induce osteoclastogenesis



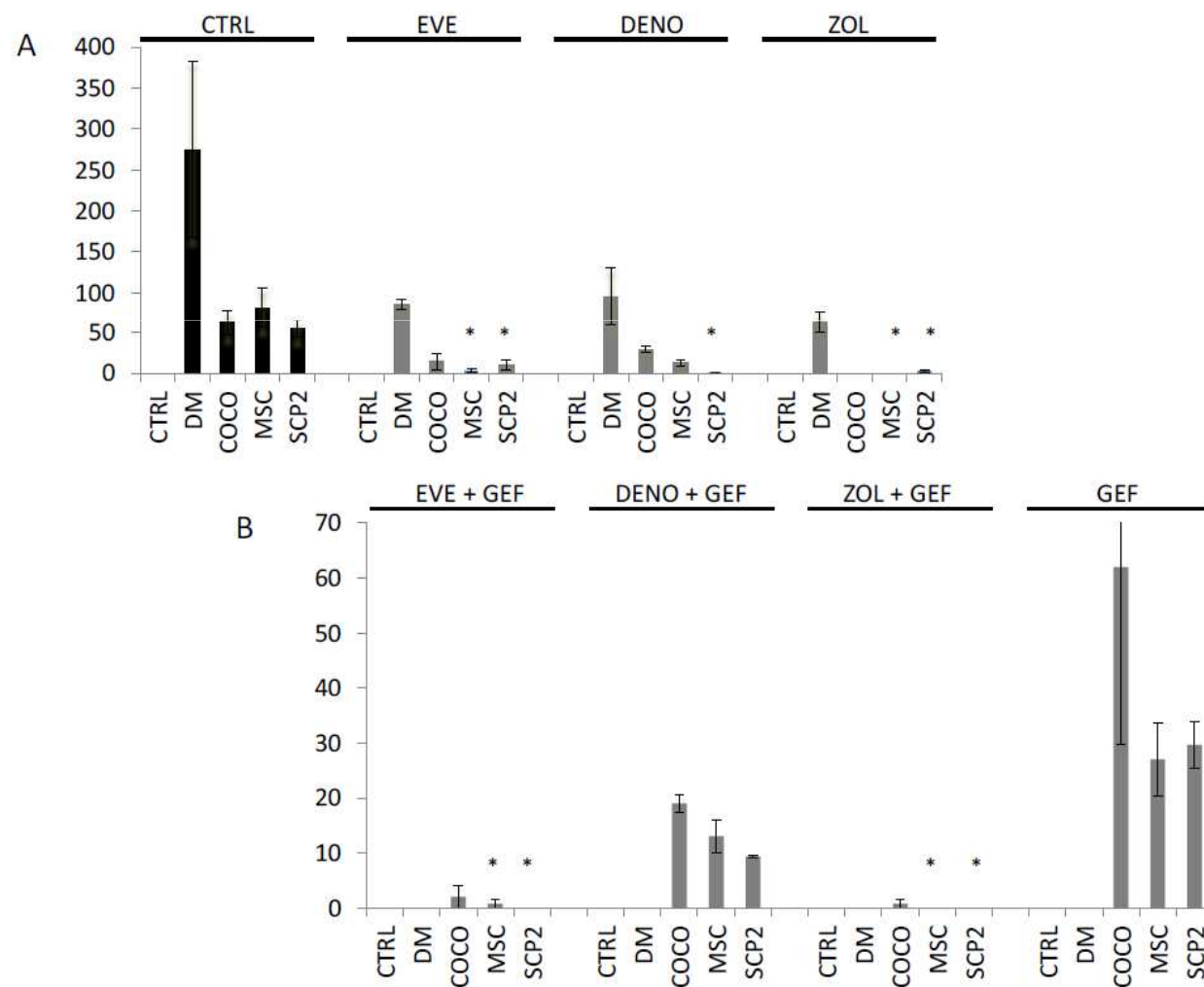


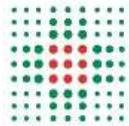
Gef impairs osteoclastogenesis induced by MSC-SCP2 COCO





Eve and Zol on osteoclasts together with Gef treatment on MSC and SCP2 totally abrogated osteoclastogenesis.



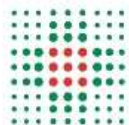


Take home messages

- This effect was enhanced by the osteoclast treatment with either Eve or Zol.

These results open the way for further investigation on the combination of conventional therapy with EGFR-targeting drugs in patients with bone metastasis.





Review

Bone Metastasis from Renal Cell Carcinoma

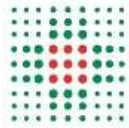
Szu-Chia Chen ^{1,2,3,4} and Po-Lin Kuo ^{1,5,*}

About one-third of patients with advanced renal cell carcinoma (RCC) have bone metastasis that are often osteolytic

The presence of bone metastasis in RCC is also associated with poor prognosis.

Bone-targeted treatment using bisphosphonate and denosumab can reduce skeletal complications in RCC, but does not cure the disease or improve survival.

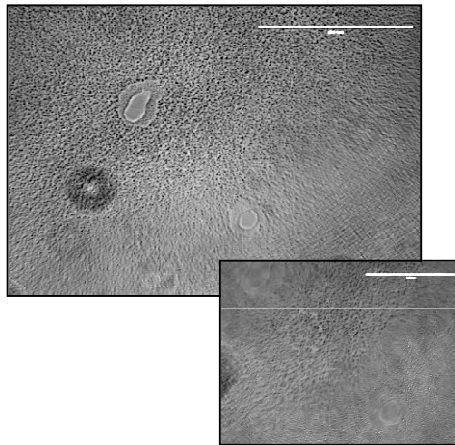
Elucidating the molecular mechanisms of tumor-induced changes in the bone microenvironment is needed to develop effective treatment.



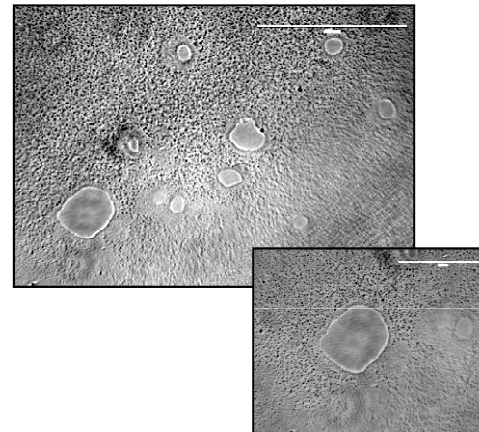
Renal cancer cell can induce osteoclastogenesis

**Pit
Assay**

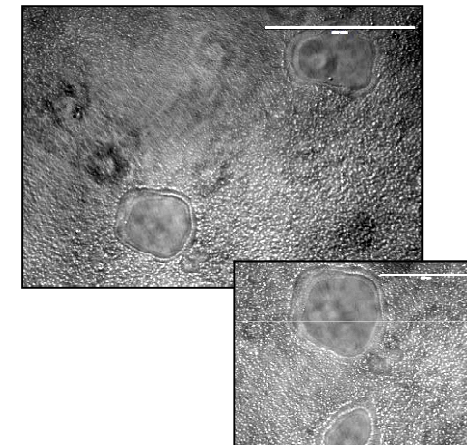
CTRL -



CTRL +

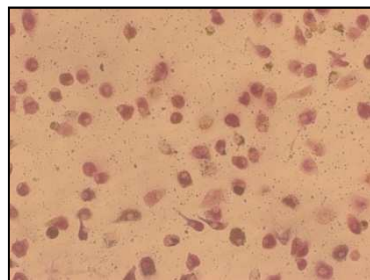


Coco Caki-2

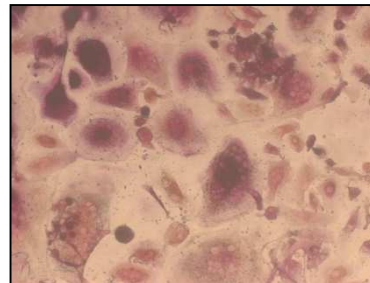


**TRAP
Staining**

CTRL -

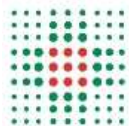


CTRL +

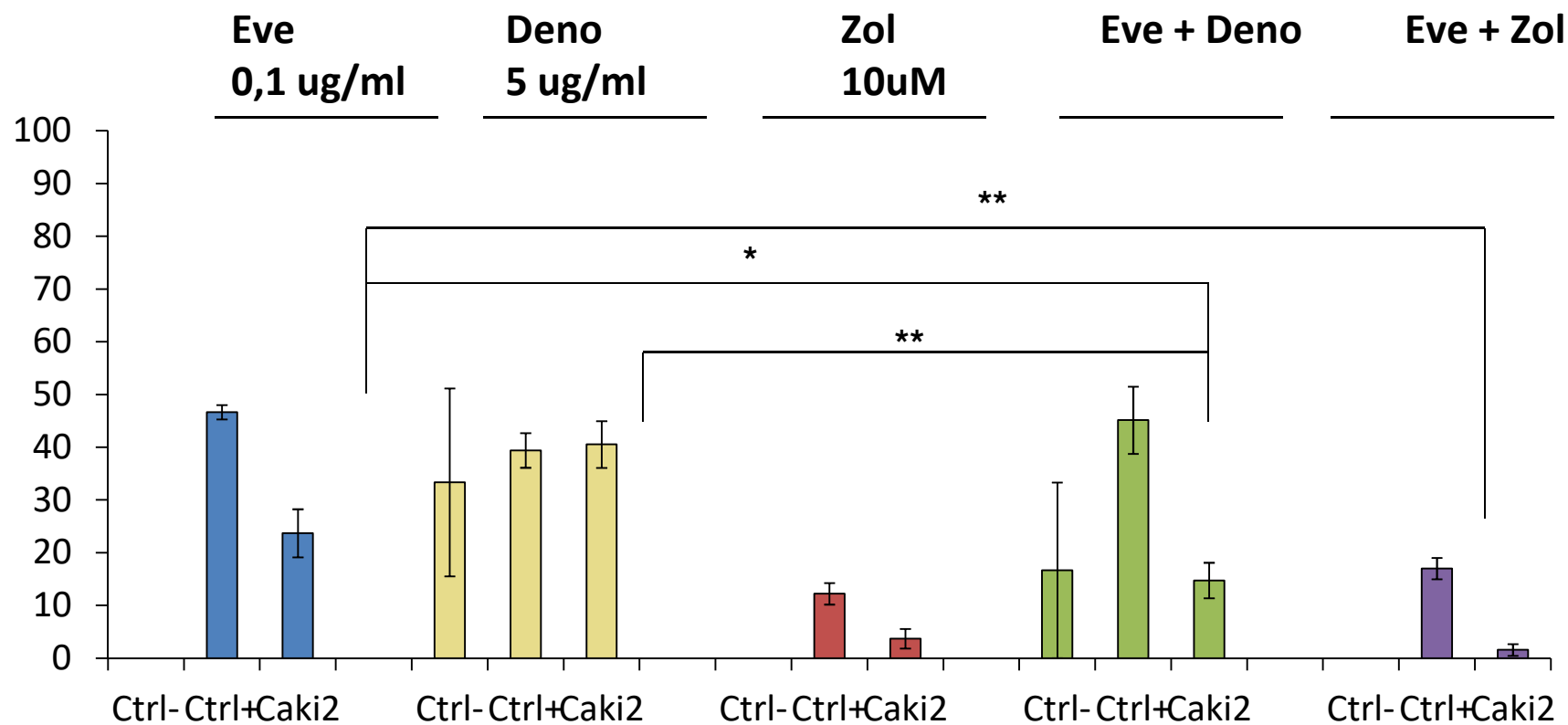


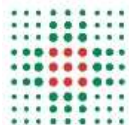
Coco Caki-2



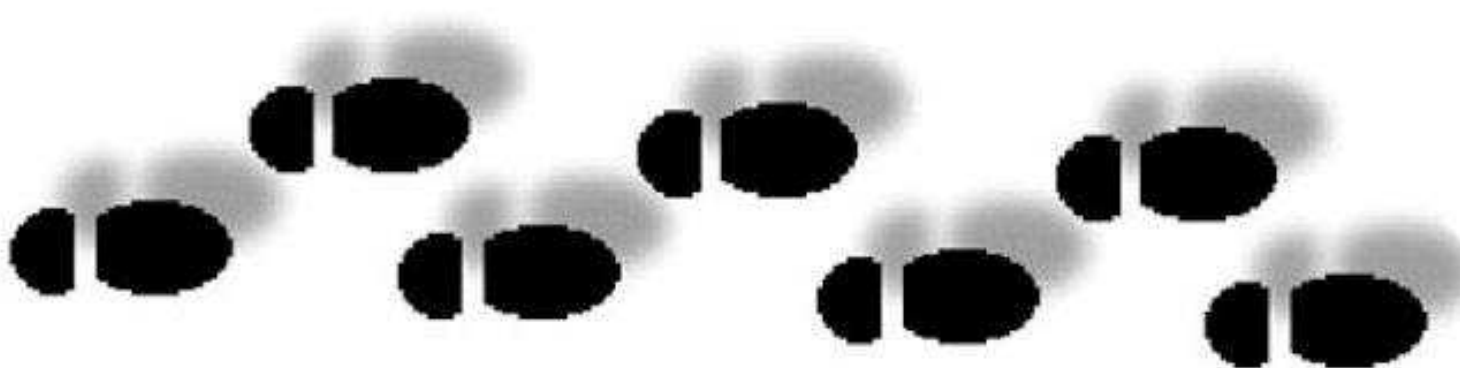
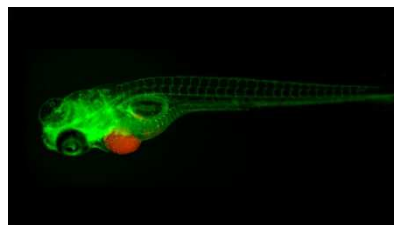
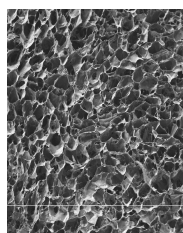


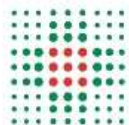
Inhibition of osteoclastogenesis





Future steps





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Centro di
Eccellenza



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Lab Researchers:
Chiara Liverani
Alessandro De Vita
Chiara Spadazzi
Giacomo Miserocchi

Specialist Nurse:
Venetia Zavoiu

Pharmacist:
Valentina Di Iorio

Oncologists:
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Nada Riva
Davide Bruschi
Sebastiano Calpona