CARCINOMA DELLA PROSTATA: MICROAMBIENTE OSSEO E PROGNOSI. LE CARATTERISTICHE DEL PAZIENTE CANDIDABILE A RADIO-223

O. Caffo

Cosa sappiamo sulla diffusione metastatica delle neoplasie prostatiche

THE DISTRIBUTION OF SECONDARY GROWTHS IN CANCER OF THE BREAST.

By STEPHEN PAGET, F.R.C.S.,
ASSISTANT SURGEON TO THE WEST LONDON HOSPITAL AND THE METROPOLITAN HOSPITAL.

AN attempt is made in this paper to consider "metastasis" in malignant disease, and to show that the distribution of the secondary growths is not a matter of chance. It is urged both by Langenbeck and by Billroth that the question ought to be asked, and, if possible, answered "What is it that decides what organs shall suffer in a case of disseminated cancer?" If the remote organs in such a case are all alike passive and, so to speak, helpless—all equally ready to receive and nourish any particle of the primary growth which may "slip through the lungs," and

Paget, S.
The distribution of secondary growths in cancer of the breast.
Lancet 1, 571–573 (1889)

Surgical Oncology (2006) 15, 117–128

Available at www.sciencedirect.com

ScienceDirect

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

REVIEW

The metastatic cascade in prostate cancer

(Initial neoplastic transformation of prostate cells)

↓

Tumour neoangiogenesis/ lymphangiogenesis and cancer growth

↓

Loss of local cell adhesion and detachment of cells from primary tumour

↓

Local invasion of host stroma (extracellular matrix)

↓

Escape of tumour cells into vasculature or lymphatics

↓

Cancer cell avoidance of immune system attack and turbulence of circulation

↓

The non-random homing of neoplastic cells to specific metastatic sites

↓

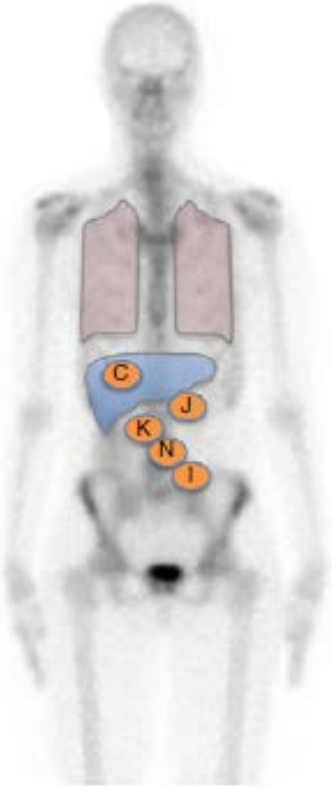
Extravasation of tumour cells into secondary organ and proliferation and growth at this site

Fidler Modern seed-and-soil hypothesis

- Tumors contain heterogeneous subpopulations of cells with different angiogenic, invasive, and metastatic properties
- The metastatic process is selective for the small subpopulation of cells that have survived the long journey to a distal organ
- The success of the metastatic cells depends on their ability to interact and utilise the “soil” provided in their new microenvironment

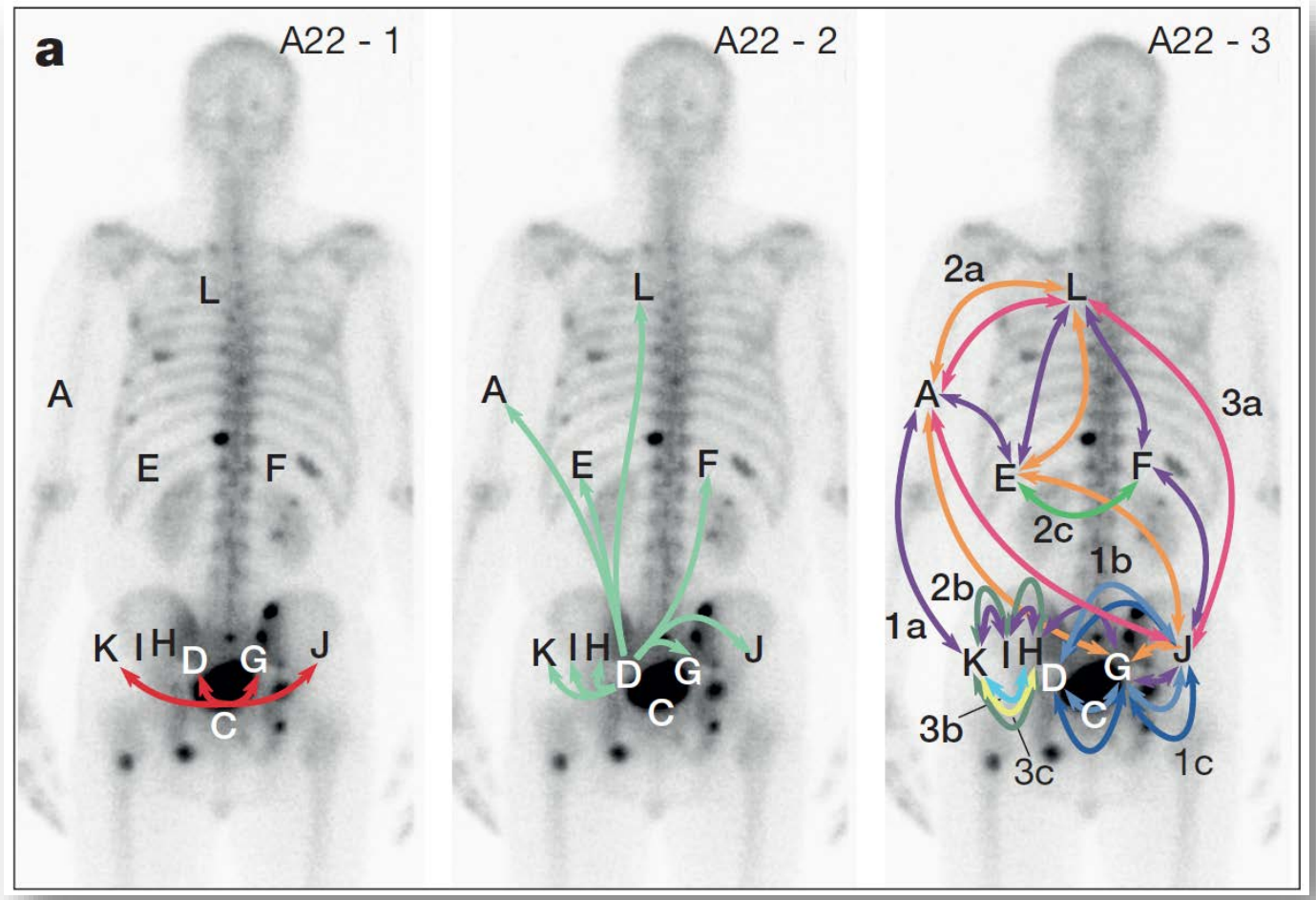
Substantial interindividual and limited intraindividual genomic diversity among tumors from men with metastatic prostate cancer

NATURE MEDICINE VOLUME 22 | NUMBER 4 | APRIL 2016



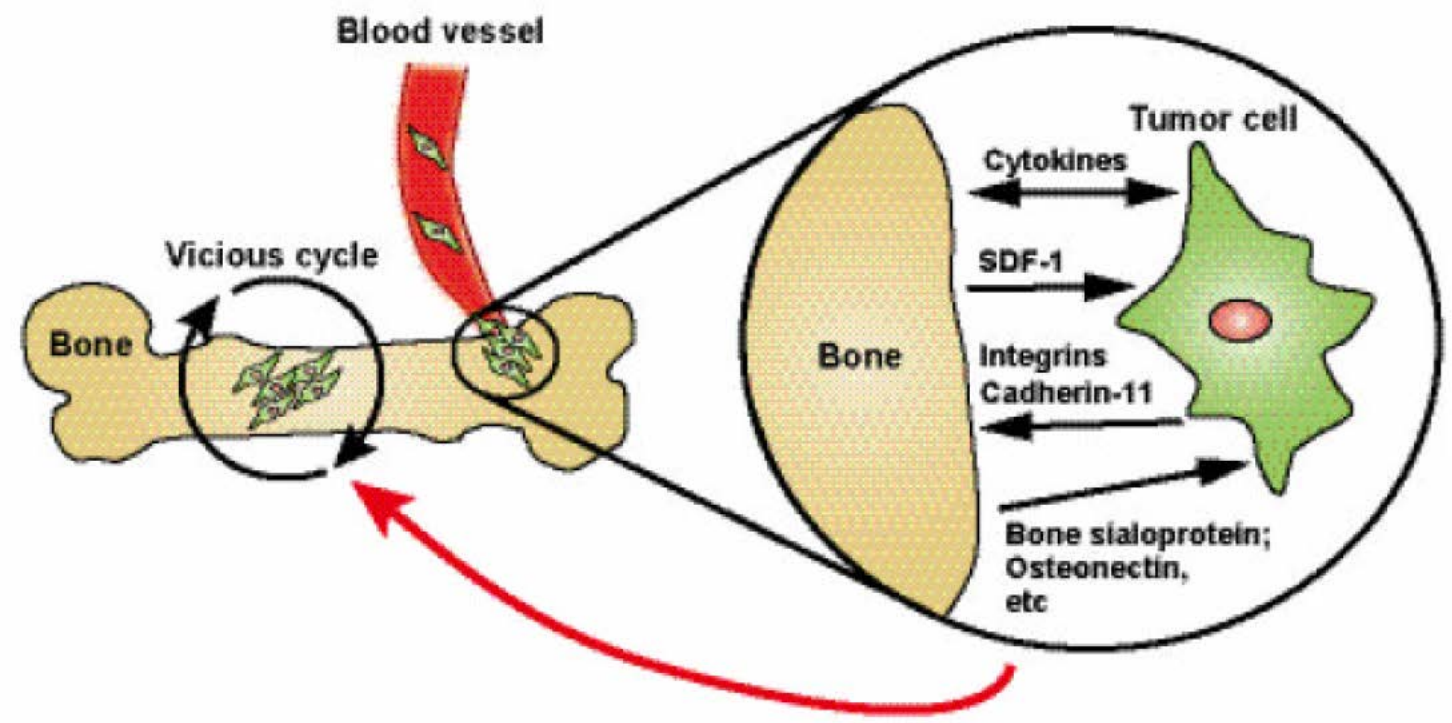
LETTER
doi:10.1038/nature14347

The evolutionary history of lethal metastatic prostate cancer

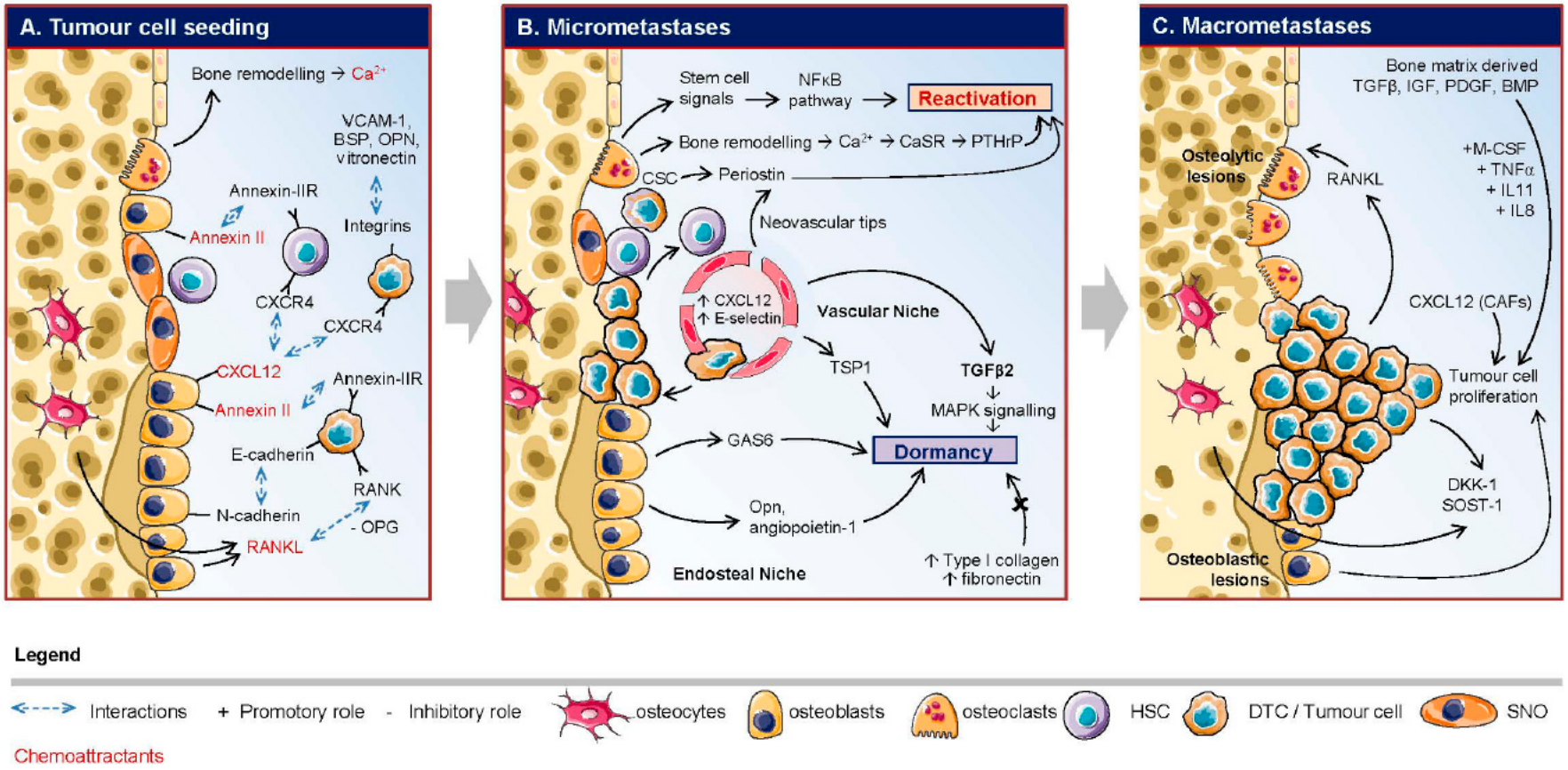


Perché lo scheletro è la principale sede di metastasi

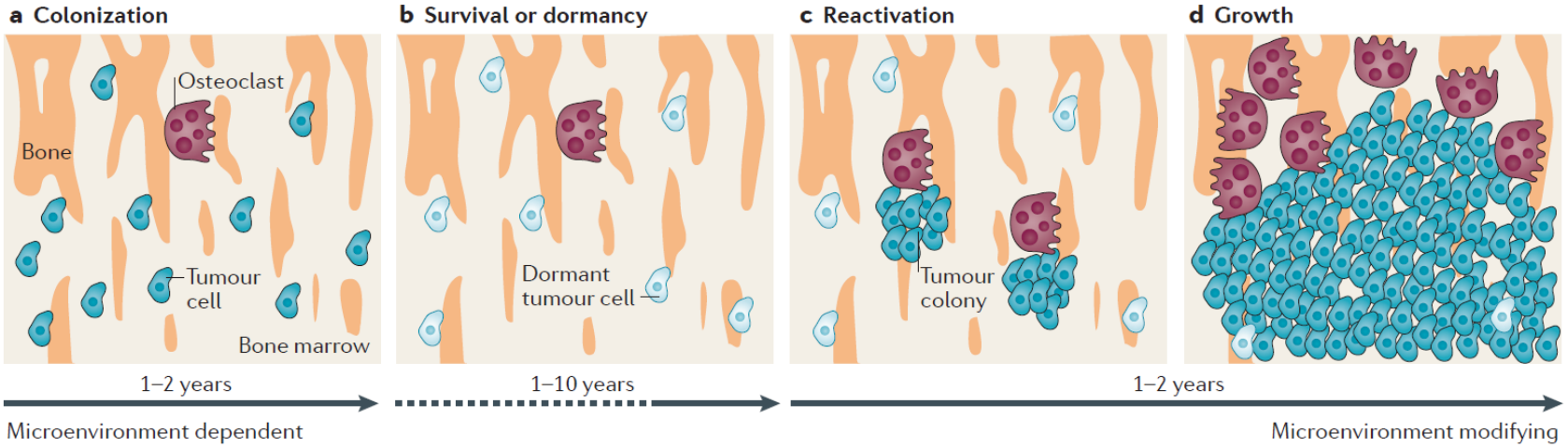
Homing and growth of prostate tumor cells in the bone could occur through factors produced or expressed in both bone and tumor.



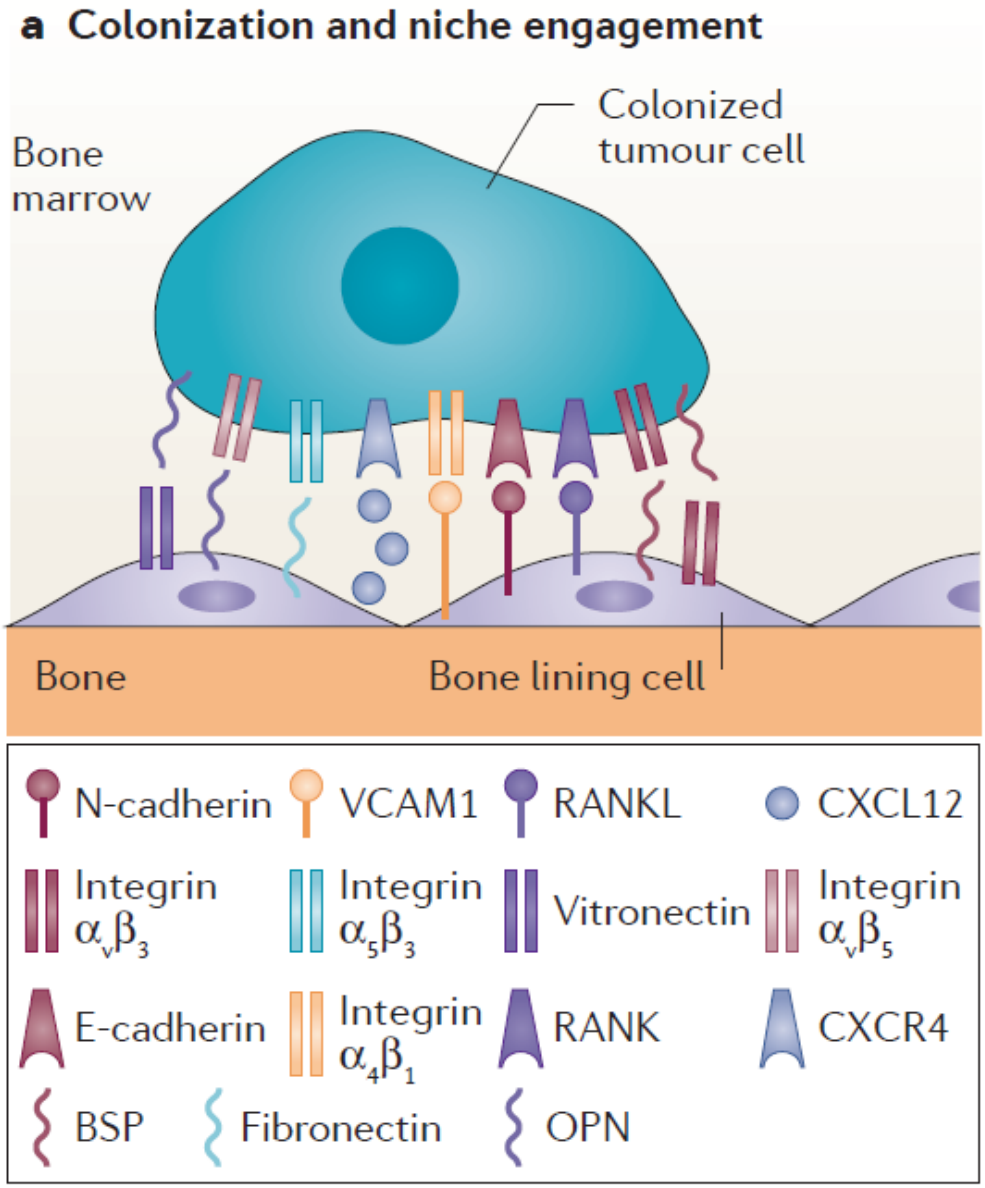
From Jin et al Int J Cancer 2011, 128: 2545



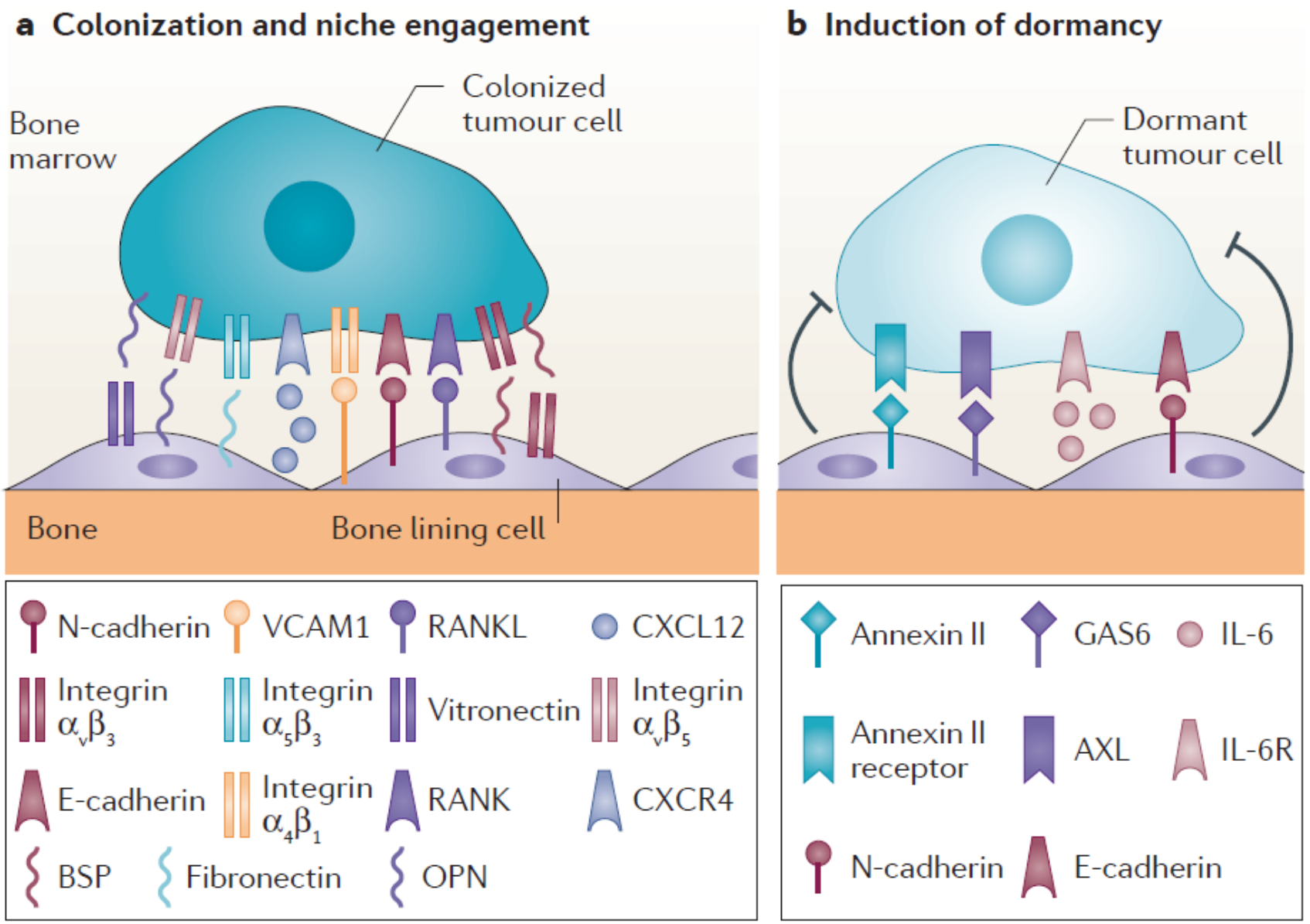
From Kan et al Int. J. Mol. Sci. 2016, 17, 1674



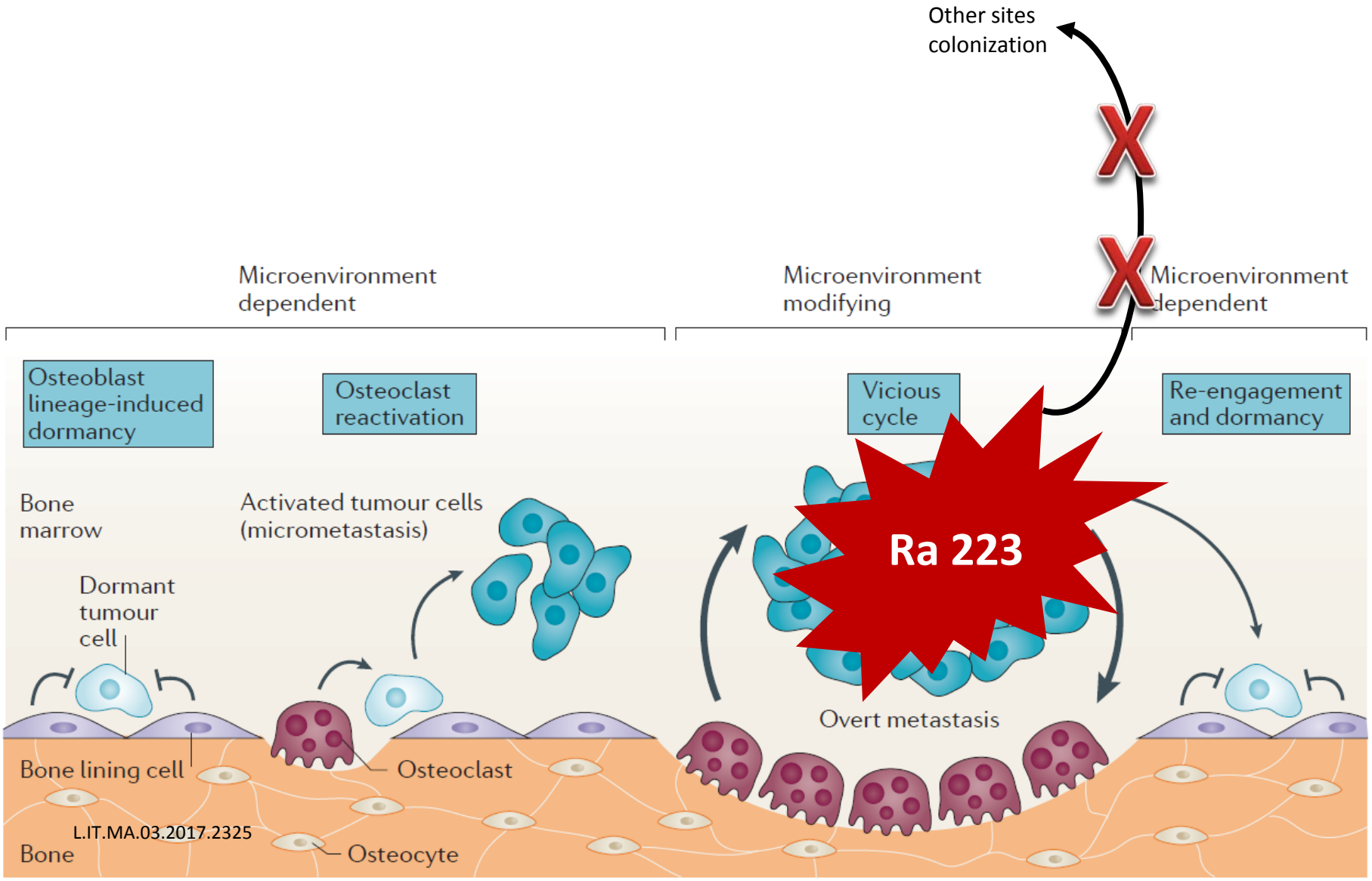
From Croucher et al Nat Rev Cancer 2016, 16, 373



Modified from Croucher et al Nat Rev Cancer 2016, 16, 373



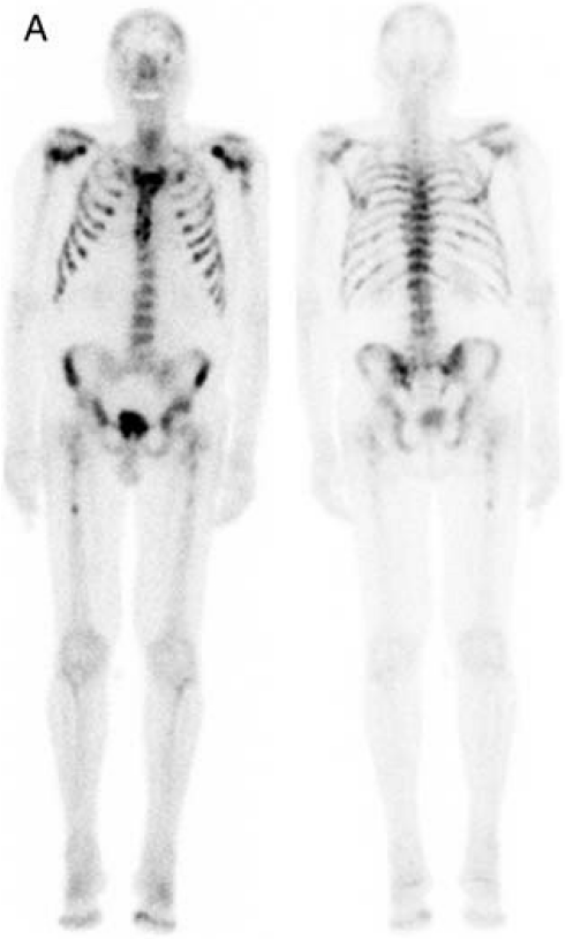
From Croucher et al Nat Rev Cancer 2016, 16, 373

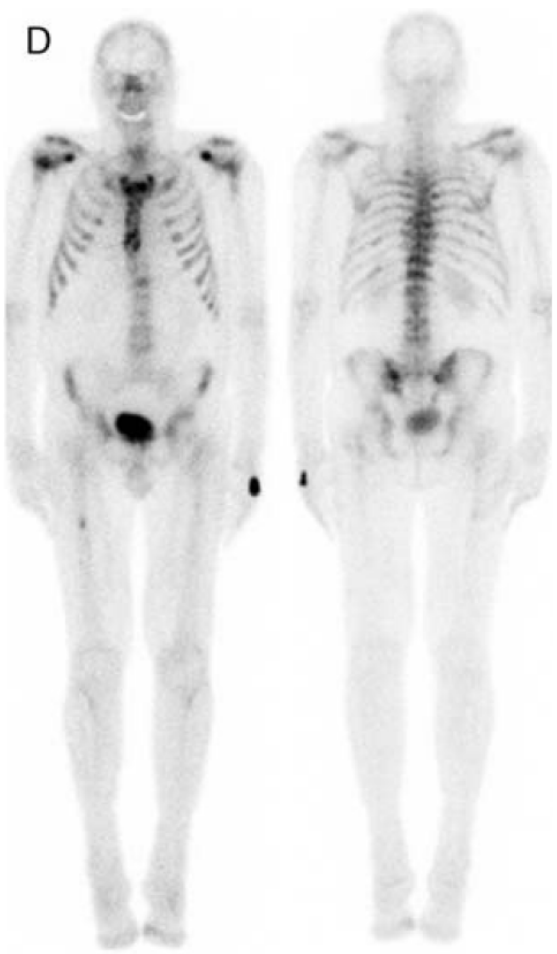


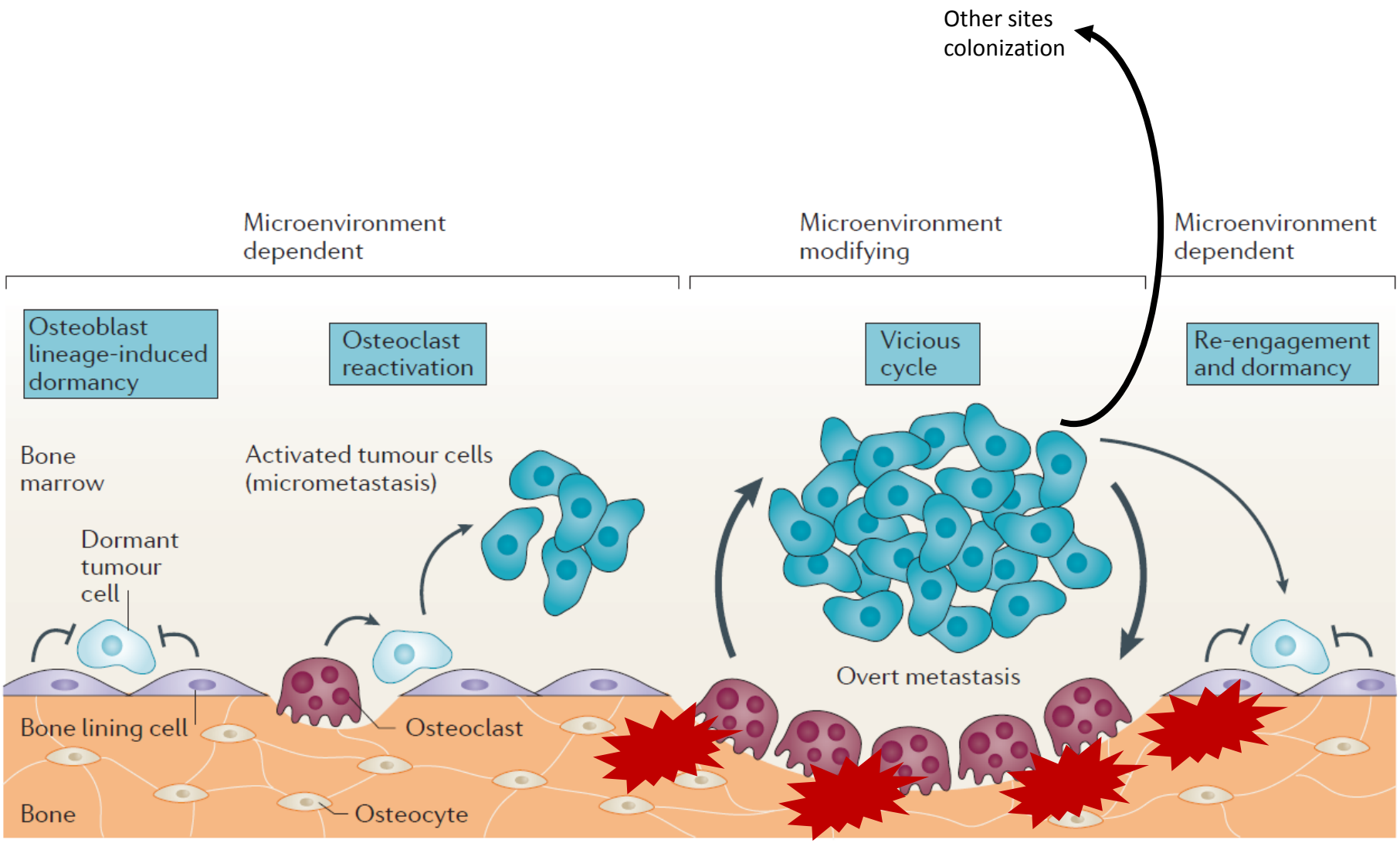
Modified from Croucher et al Nat Rev Cancer 2016, 16, 373

^{68}Ga-PSMA-11 PET Represents the Tumoricidal Effect of ^{223}Ra in a Patient With Castrate-Resistant Metastatic Prostate Cancer

Clin Nucl Med 2016;41: 695–696







Modified from Croucher et al Nat Rev Cancer 2016, 16, 373

La prognosi delle neoplasie prostatiche è influenzata dalla sede delle metastasi?

EUROPEAN UROLOGY 65 (2014) 3–6

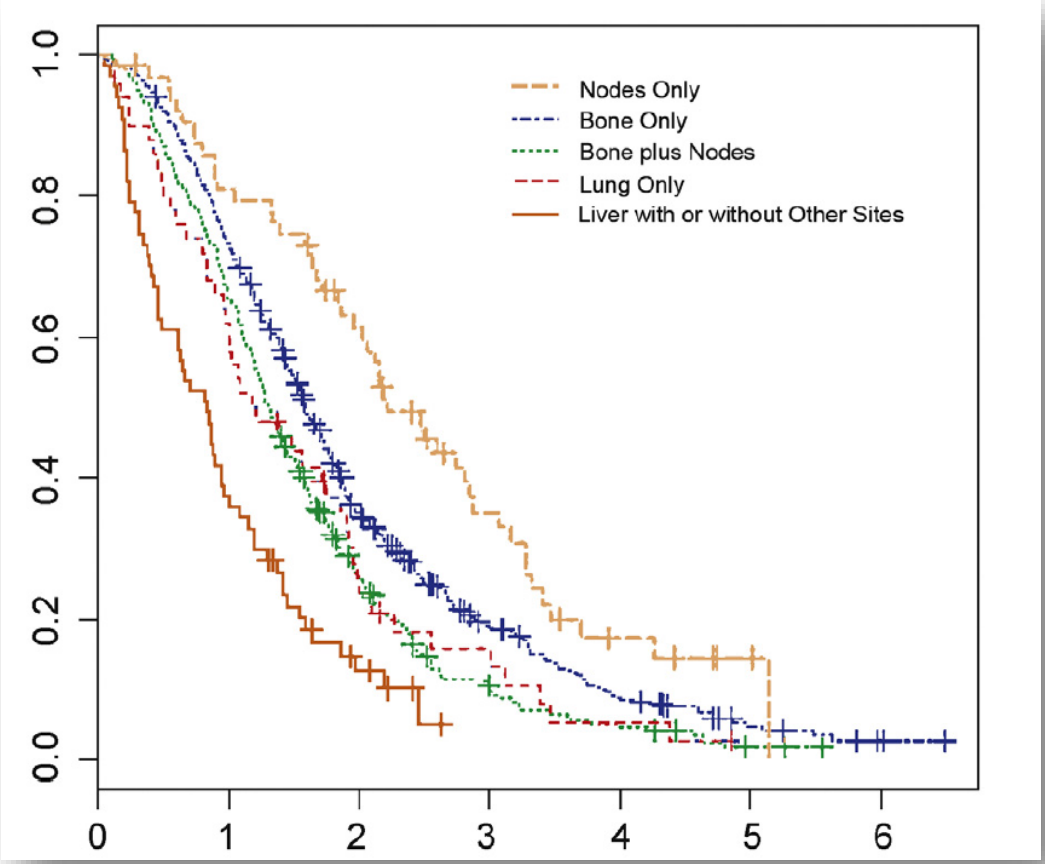
available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

The Prognostic Importance of Metastatic Site in Men with Metastatic Castration-resistant Prostate Cancer

TAX 327 population



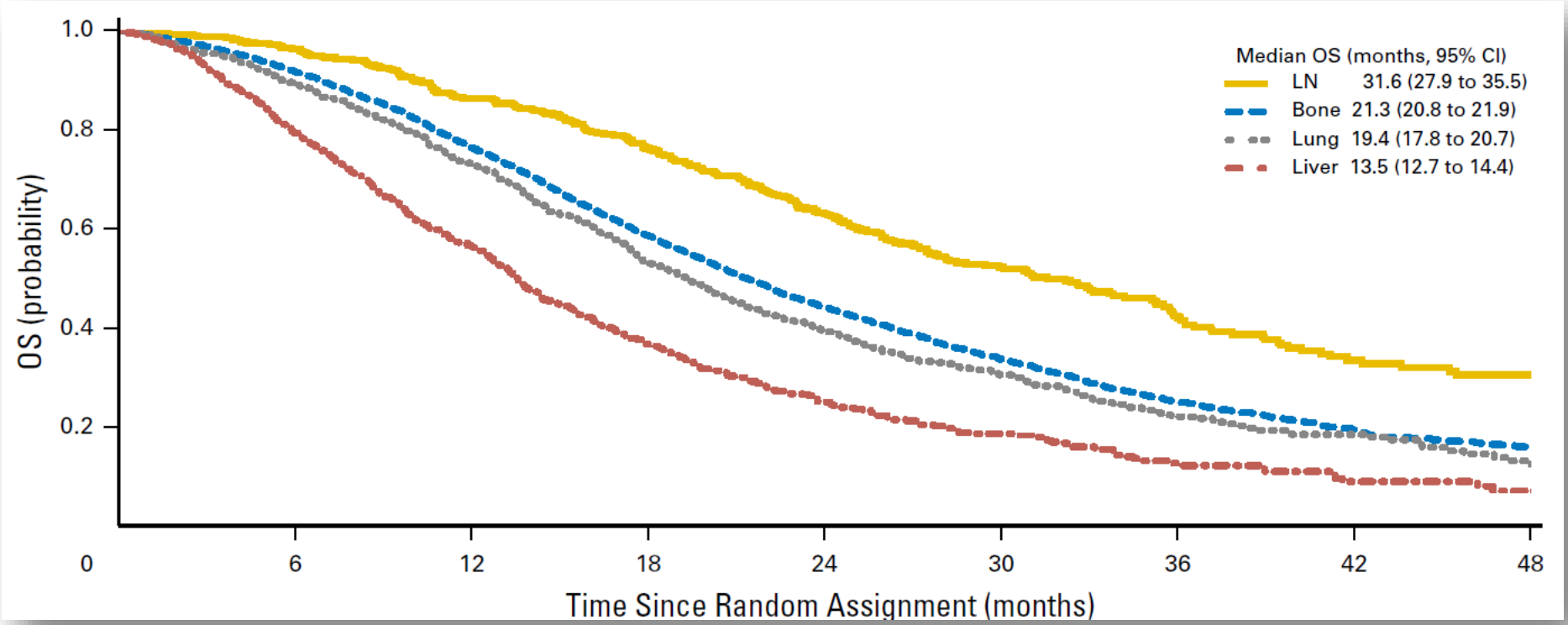
VOLUME 34 · NUMBER 14 · MAY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men With Castration-Resistant Prostate Cancer

8,820 mCRPC pts
9 phase III trials



EUROPEAN UROLOGY 68 (2015) 325–334

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

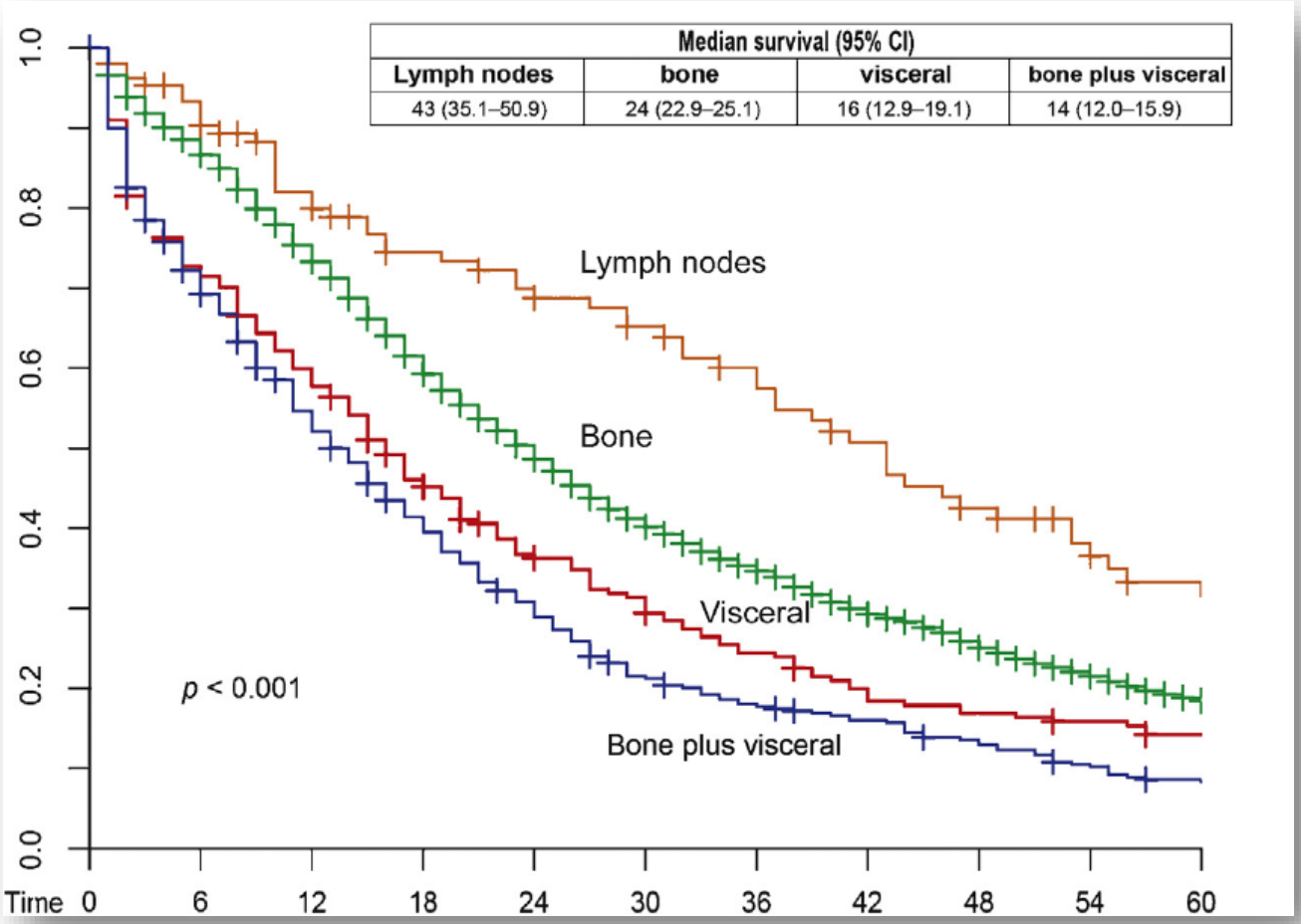
European Association of Urology

Prostate Cancer

Impact of the Site of Metastases on Survival in Patients with Metastatic Prostate Cancer

3,857 mPCa pts SEER database

Median survival (95% CI)			
Lymph nodes	bone	visceral	bone plus visceral
43 (35.1–50.9)	24 (22.9–25.1)	16 (12.9–19.1)	14 (12.0–15.9)



Mortality following bone metastasis and skeletal-related events among men with prostate cancer: a population-based analysis of US Medicare beneficiaries, 1999–2006

Prostate Cancer and Prostatic Diseases (2011) 14, 177–183

Variable in Cox regression model	*Deaths/PY*	*HR*	*95% CI*
Bone metastasis at or subsequent to diagnosis			
None	22 639/433 319	1.0 (referent)	—
Yes, without SREs	3807/6965	6.6	(6.4, 6.9)
Yes, with SREs	3274/4275	10.2	(9.8, 10.7)

Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomised, multicentre, placebo-controlled phase II study

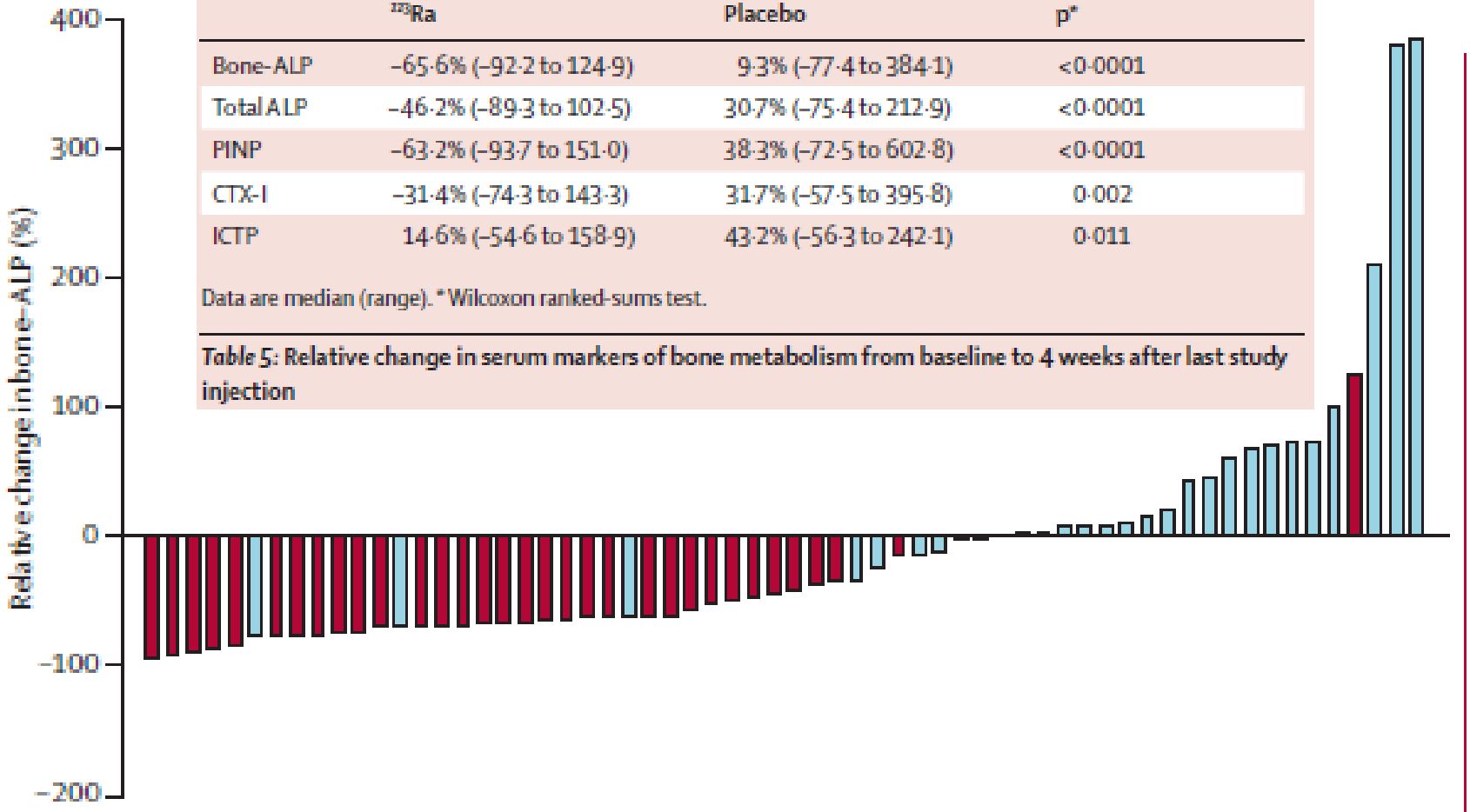
http://oncology.thelancet.com Vol 8 July 2007

Nilsson S et al

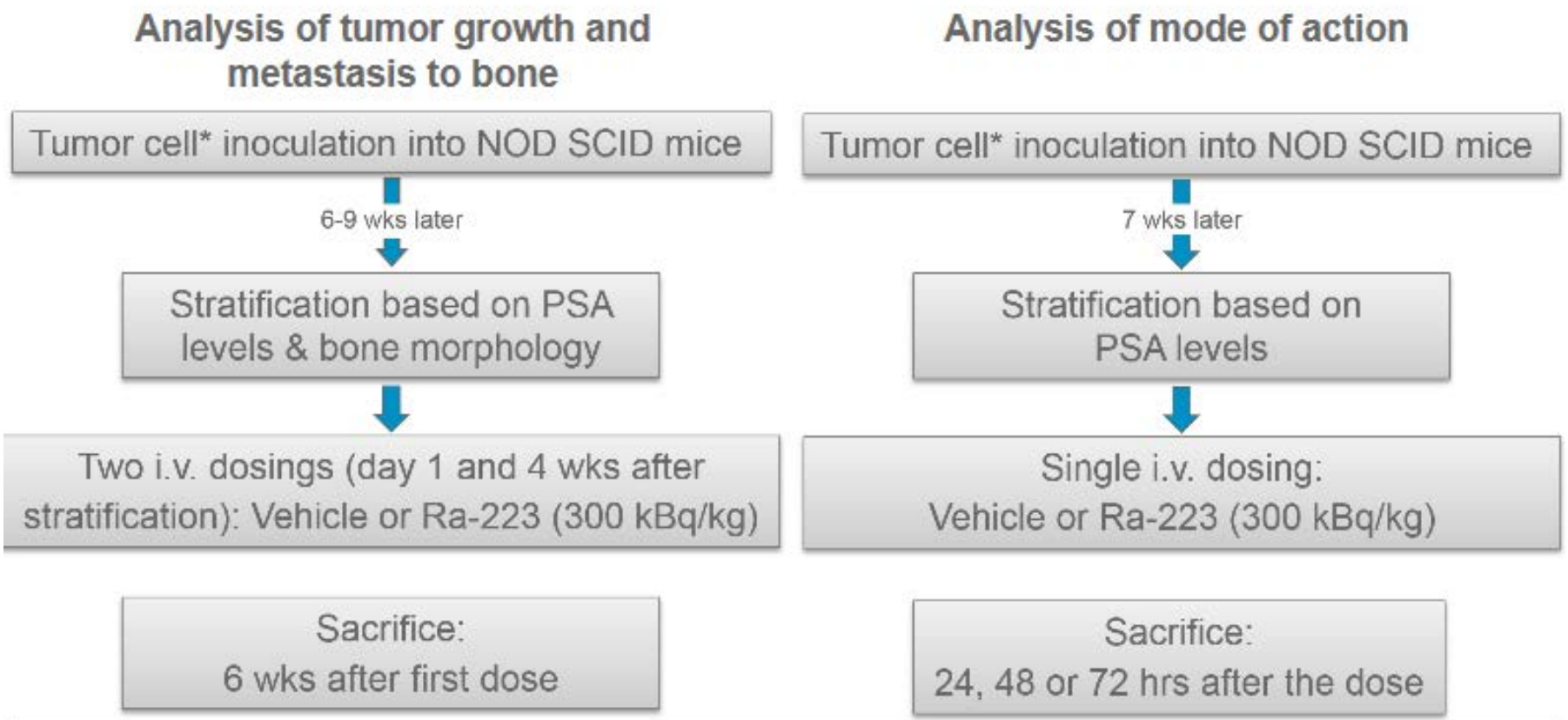
	^{223}Ra	Placebo	p*
Bone-ALP	−65·6% (−92·2 to 124·9)	9·3% (−77·4 to 384·1)	<0·0001
Total ALP	−46·2% (−89·3 to 102·5)	30·7% (−75·4 to 212·9)	<0·0001
PINP	−63·2% (−93·7 to 151·0)	38·3% (−72·5 to 602·8)	<0·0001
CTX-I	−31·4% (−74·3 to 143·3)	31·7% (−57·5 to 395·8)	0·002
ICTP	14·6% (−54·6 to 158·9)	43·2% (−56·3 to 242·1)	0·011

Data are median (range). * Wilcoxon ranked-sums test.

Table 5: Relative change in serum markers of bone metabolism from baseline to 4 weeks after last study injection



Study designs for investigating the therapeutic effects of Ra-223

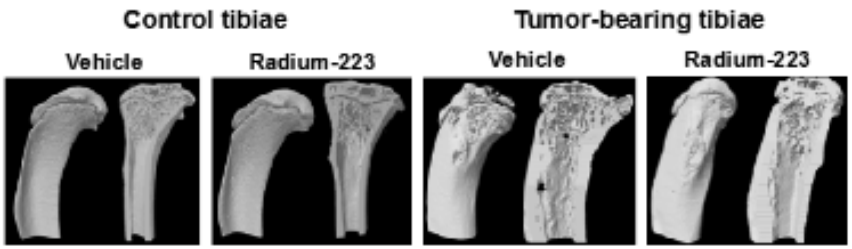


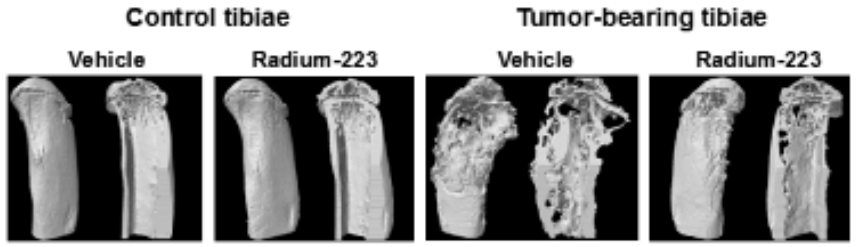
*Two clinically-relevant prostate cancer xenograft models were used:

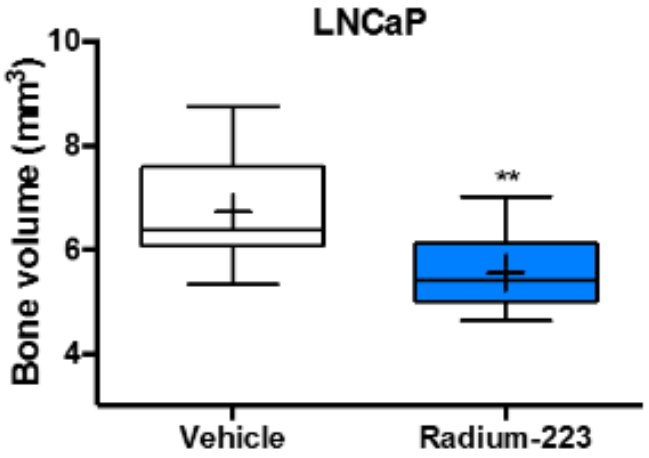
- LNCaP cell-line model
- *Abiraterone resistant* LuCaP 58 patient-derived xenograft (PDX) model

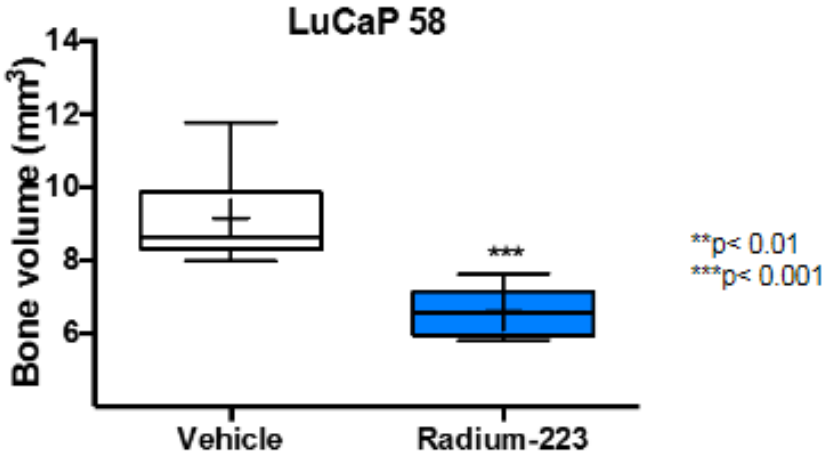
Suominen et al. Clin Can Res 2017

Ra-223 inhibits tumor-induced osteoblastic reaction resulting from LNCaP and LuCaP 58 prostate cancer growth in bone





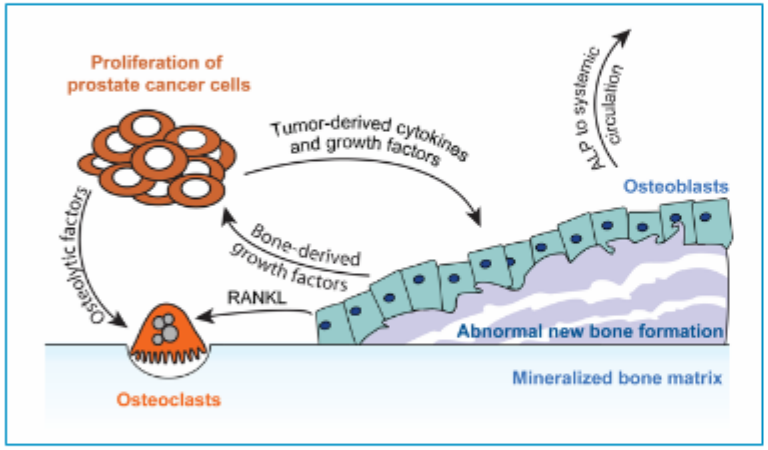


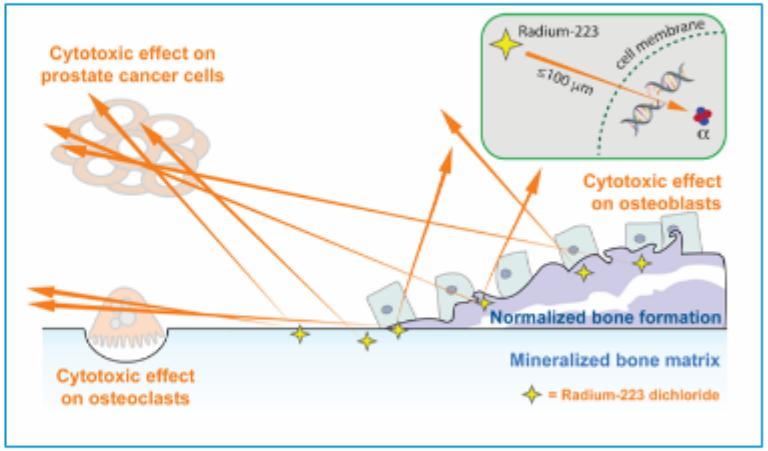


- **Ra-223 inhibits disease progression in both models.**
- **Ra-223 inhibits tumor-induced bone formation and protects normal bone architecture.**

Suominen et al. Clin Can Res 2017

Ra-223 therapy exhibits a dual mode-of-action

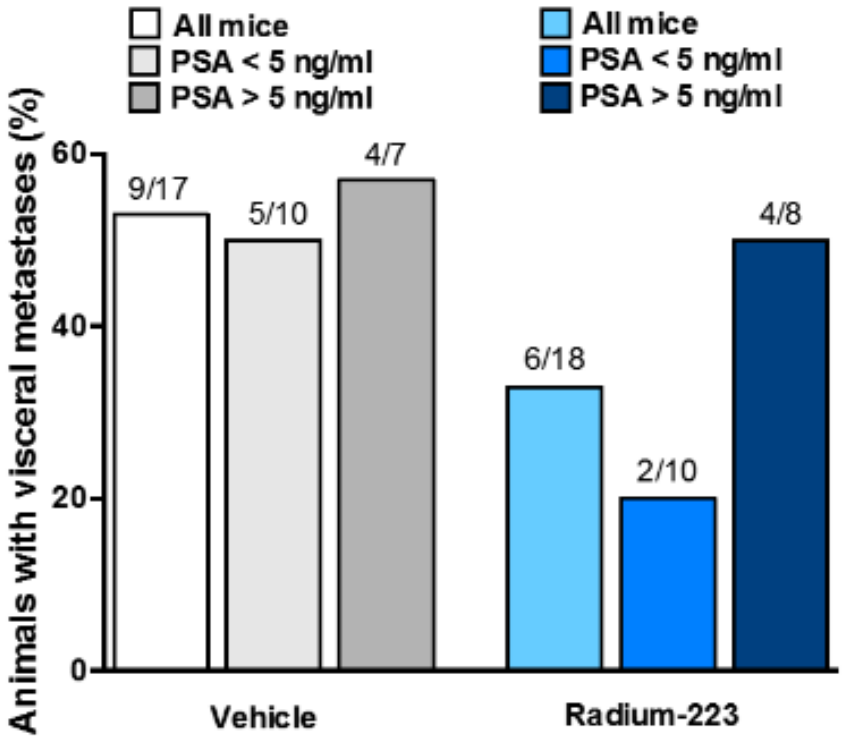




- **Ra-223 therapy exhibits a dual mode-of-action by destroying tumor cells as well as inhibiting tumor-induced pathological bone reaction.**

Suominen et al. Clin Can Res 2017

The effect of Ra-223 treatment on visceral metastases in LuCaP 58 prostate cancer PDX model



- **Ra-223 may attenuate the development of visceral metastases.**

Suominen et al. Clin Can Res 2017

Come possiamo selezionare i pazienti per il trattamento con radium 223

Ra-223: indicazione approvata

Posologia

Il regime posologico di Ra-223 dicloruro consiste in un'attività di 55 kBq per kg di peso corporeo, somministrata ad intervalli di 4 settimane per 6 iniezioni

Indicazione
La somministrazione di Ra-223 dicloruro è indicata per il trattamento di pazienti affetti da carcinoma prostatico resistente alla castrazione (CRPC), con metastasi ossee sintomatiche, senza metastasi viscerali note.

Assunzione occasionale di analgesici — **Paz. sintomatico** — **Assunzione regolare di oppioidi**

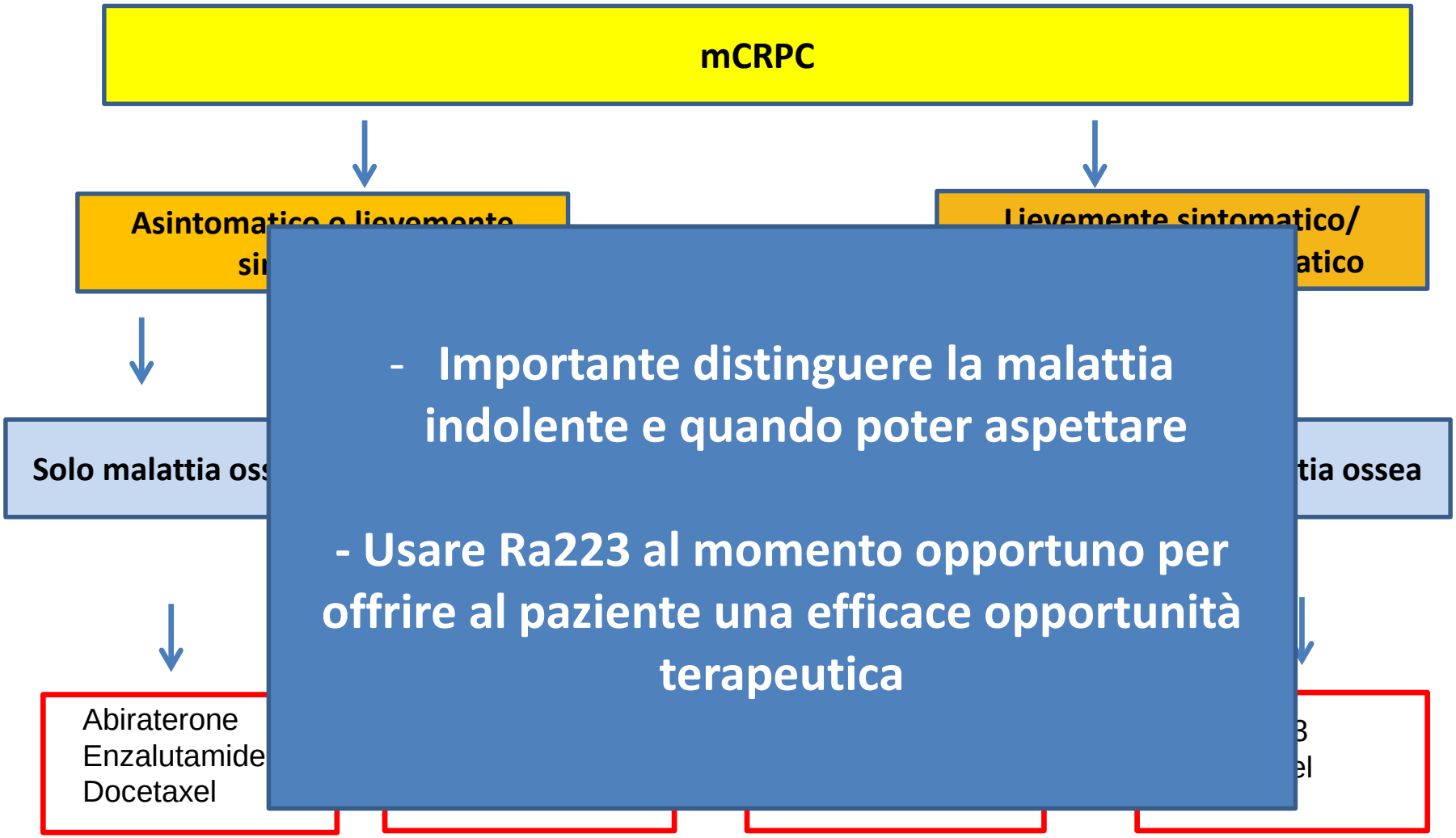
Poche metastasi — **Metastasi ossee** — **Superscan**

Solo linfonodi <3cm — **Metastasi viscerali** — **Non è consentito l'uso in caso di metastasi viscerali**

Parker C, et al. N Engl J Med. 2013;369:213-223.Xofigo, Riassunto Caratteristiche del prodotto

Come scegliere il trattamento?

Scenario Terapeutico 2015 - mCRPC



Grandangolo 2015

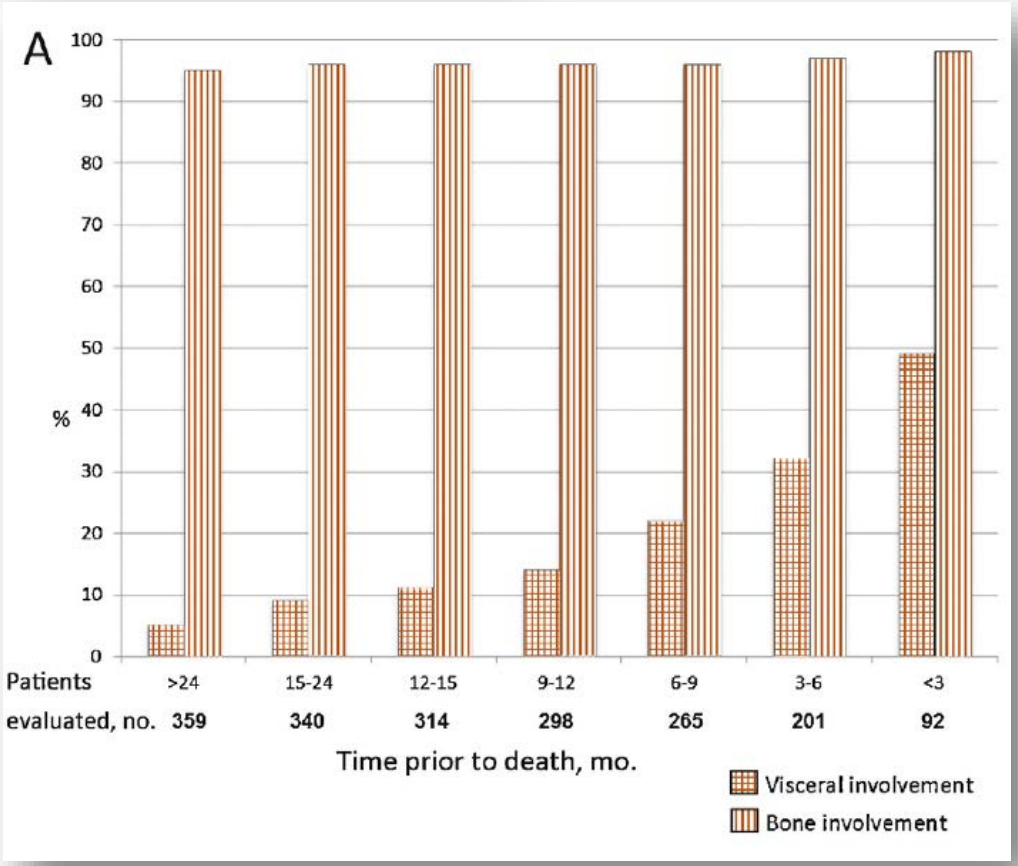
EUROPEAN UROLOGY 65 (2014) 270–273

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

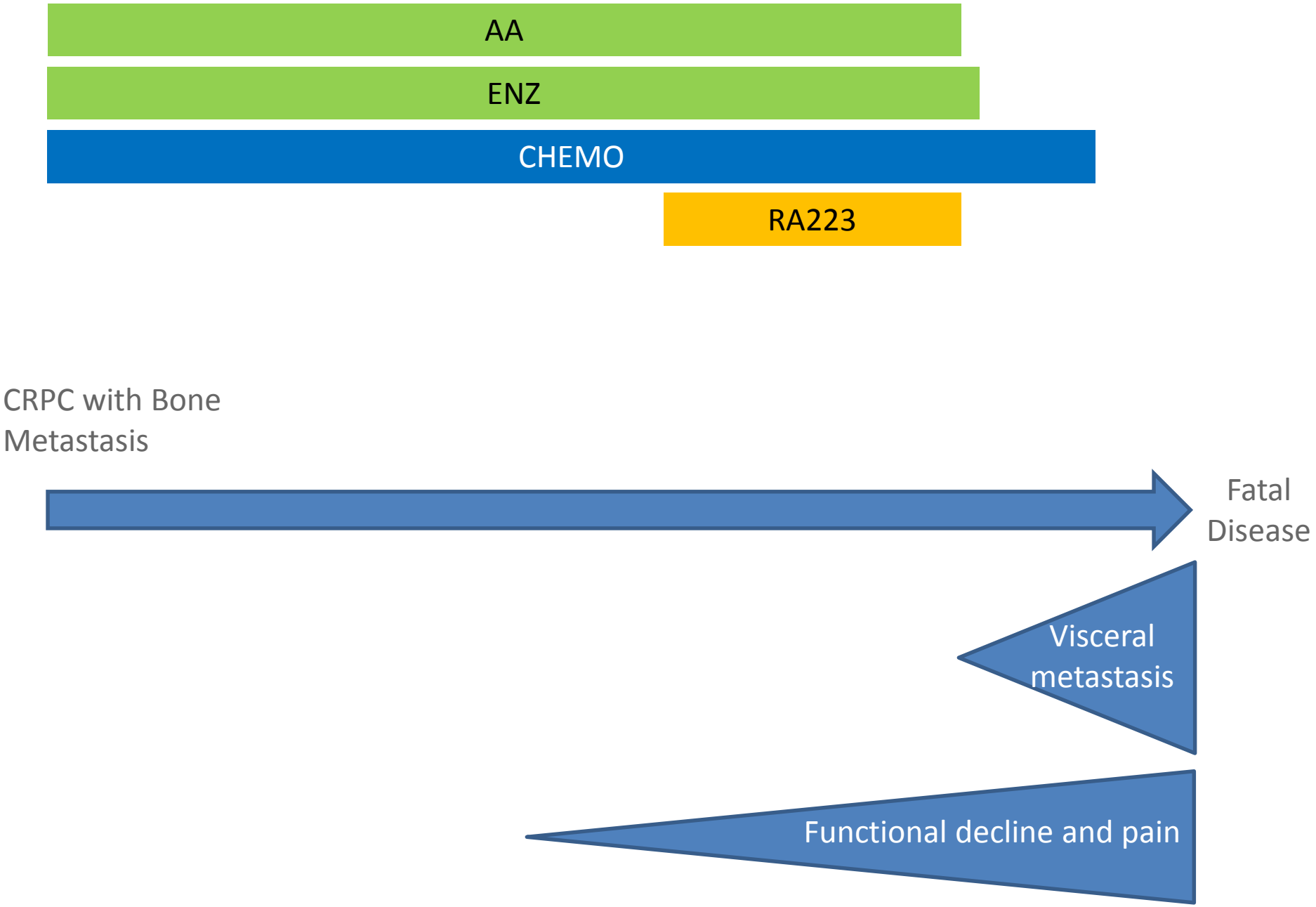
European Association of Urology

Brief Correspondence

Visceral Disease in Castration-resistant Prostate Cancer



- Carico di malattia
- Dolore
- Cinetica del PSA
- Sviluppo delle metastasi
- Strategia terapeutica
- Riserva midollare


AA
ENZ
CHEMO
RA223
CRPC with Bone Metastasis
Fatal Disease
Visceral metastasis
Functional decline and pain