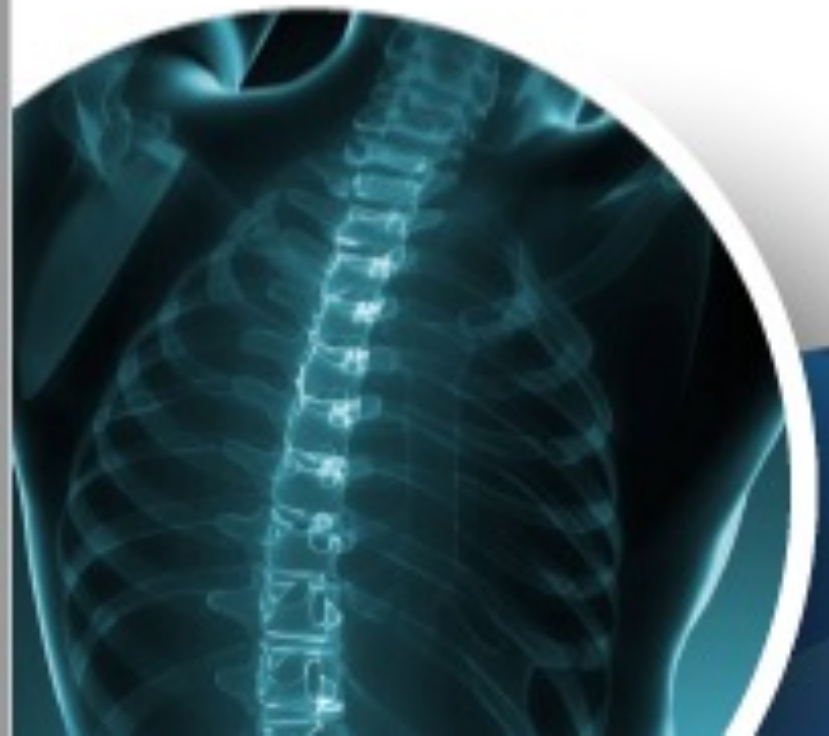
21 giugno 2021
WEBINAR

METASTASI OSSEE
DA TUMORE POLMONARE:
UNA SEDE METASTATICA
TROPPO POCO ENFATIZZATA

Responsabili Scientifici: Alessandro Del Conte e Gaetano Lanzetta



Il carcinoma polmonare con lesioni scheletriche nell'era della target therapy

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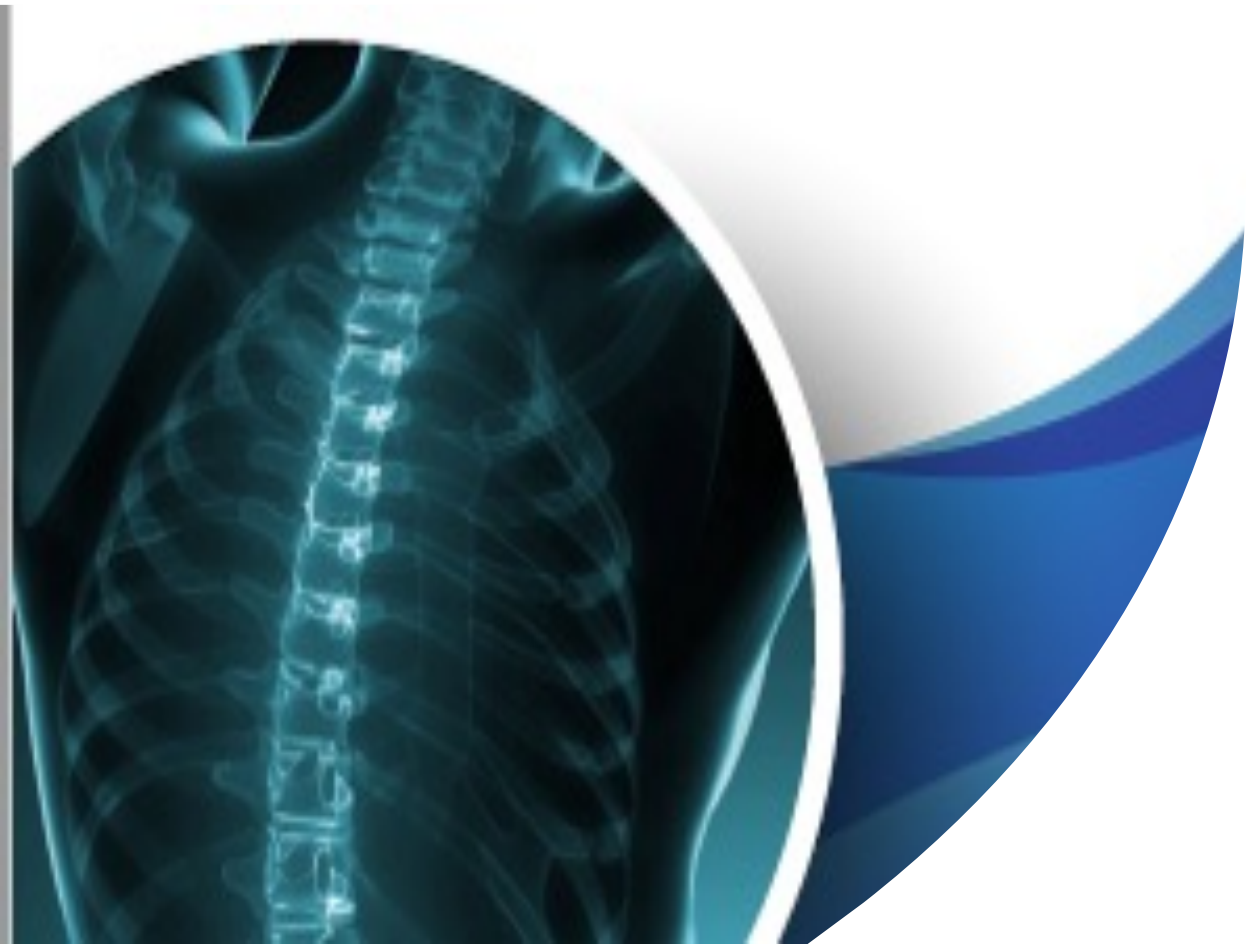
Oncologia Toracica – Lung Unit

Ospedale Pederzoli (Peschiera d/G – VR)

AGENDA



- Introduction
- The era of target therapy
- Future in the era of target therapy
- The real life in the era of target therapy
- Take of message

INTRODUCTION

Bone metastases in NSCLC

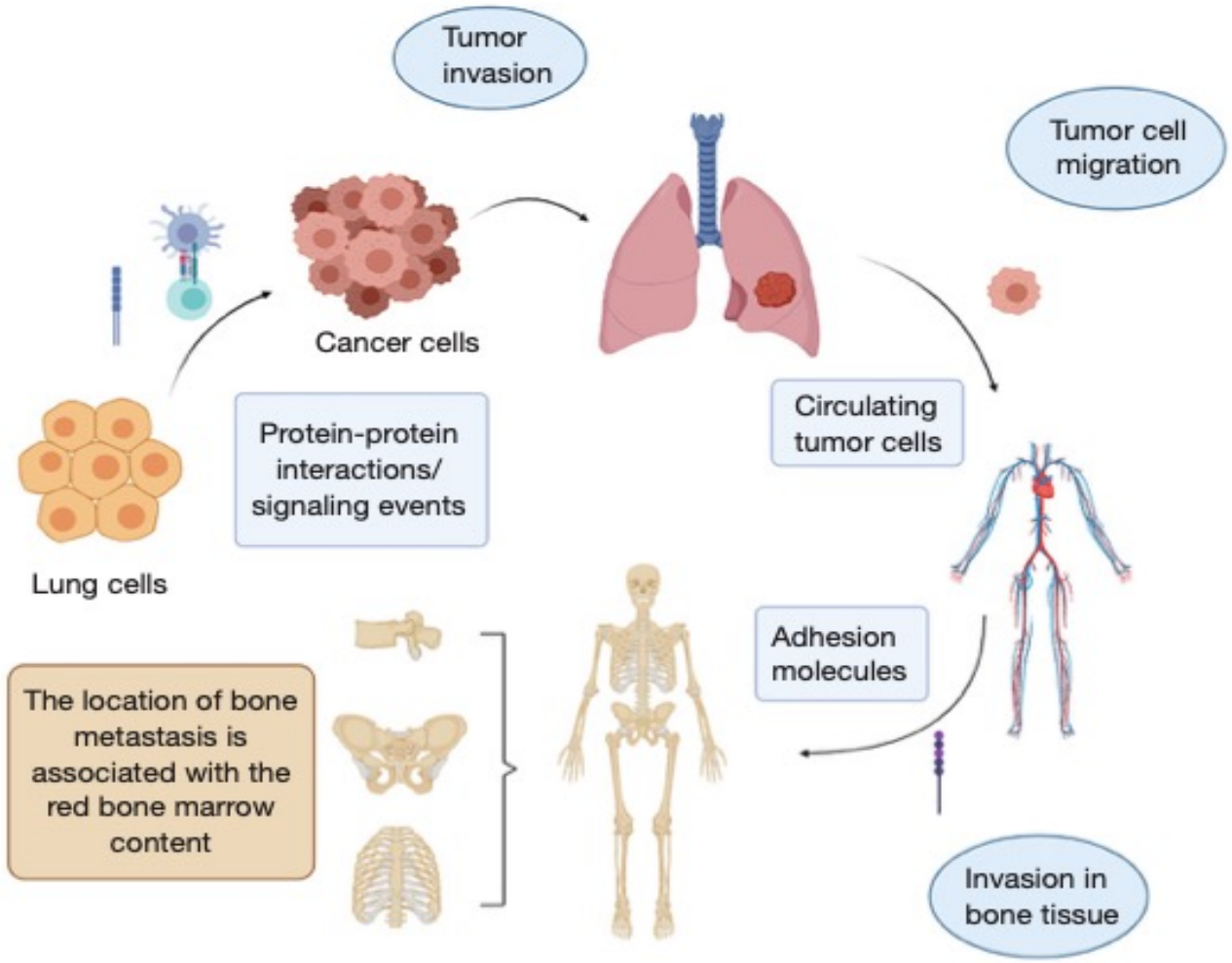
- NSCLC bone M+ median OS is <6 months and 5 years OS rate is <5%
- NSCLC = third most common cause of bone metastases (I:breast, II:prostate cancer)

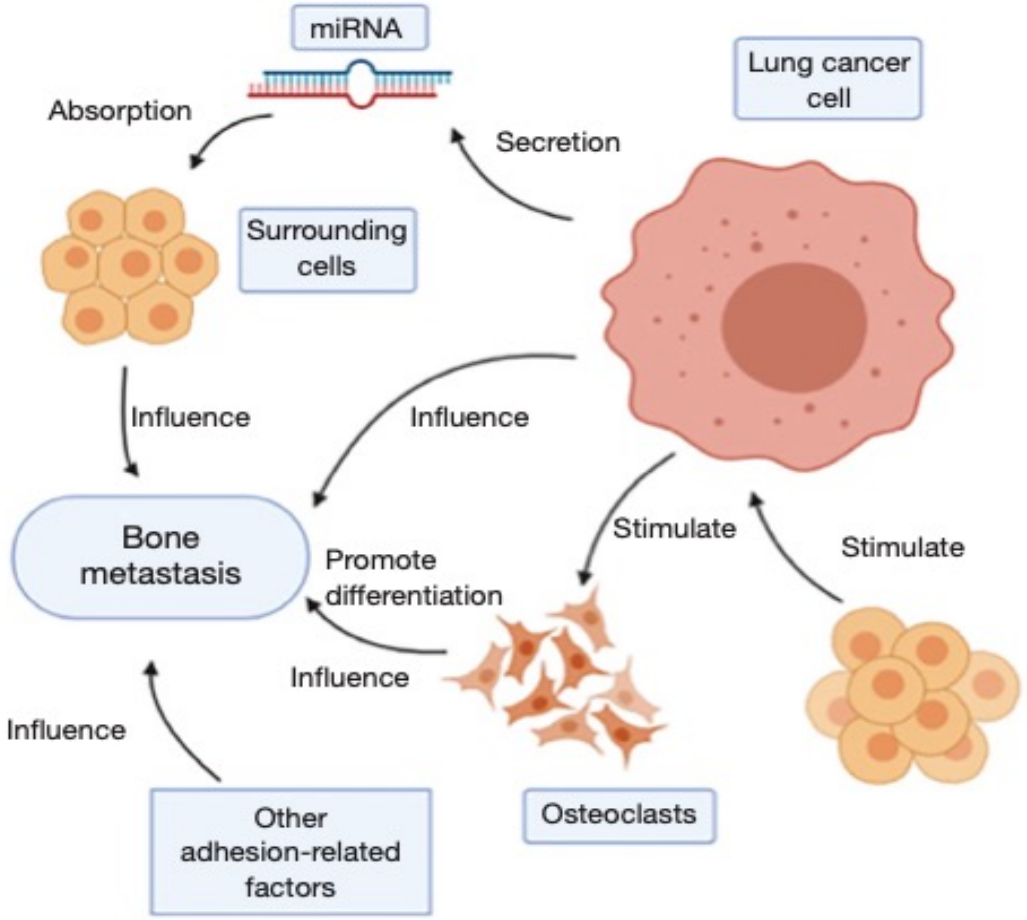
- Incidence of bone metastasis in NSCLC
  - 30–40% during the clinical course
  - 60% at the time of diagnosis
- Presence of bone metastases → poor prognosis
- Bone metastases have a greater negative impact on the OS and the QoL

Rosen, Cancer. (2004).
Price, N., Clin Lung Cancer. (2004)
Kosteva, J. Lung Cancer. (2004)
Coleman, Cancer. (1997)
Weinfurt, K. P. Ann Oncol. (2005)
Lipton, A. Cancer. (2000).
Torre LA, et al; *CA a cancer J Clin*. (2015)
Yu JL, **et al;** *Oncologist*. (@)!!)

INTRODUCTION

The process of bone metastasis in lung cancer



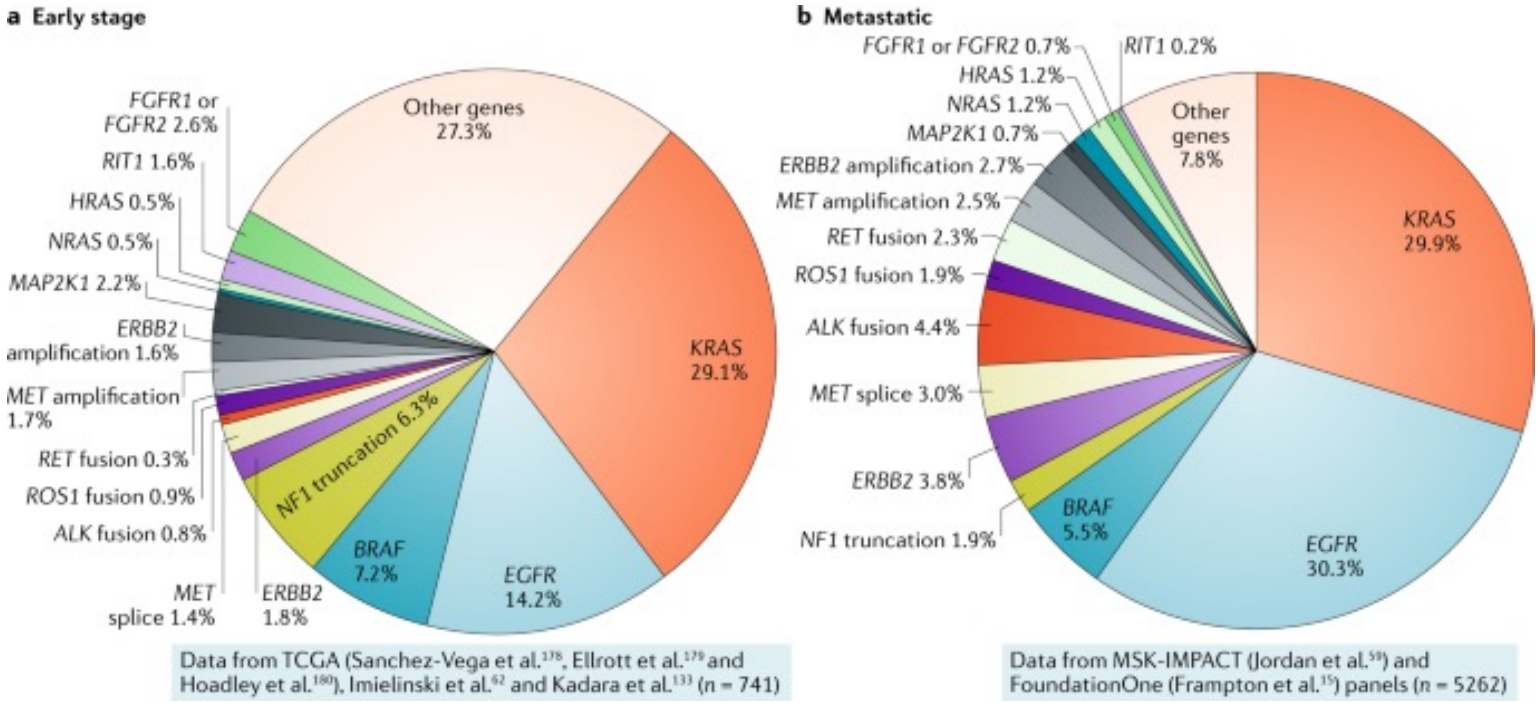


Transl Lung Cancer Res 2021

THE ERA OF TARGET THERAPY

NSCLC ADK

EGFR | ALK | ROS 1 | BRAF | KRAS



Skoulidis, Nature Reviews Cancer 2019

THE ERA OF TARGET THERAPY

Bone metastases in NSCLC

Reference	Total number of patients	BM+ at diagnosis	ADK BM+	Squamo BM+	Treatment of NSCLC	Treatment of BM	PFS	OS
Rosen, 2003	280	280 (100%)	nd	nd	nd	Biphosphonates	nd	6.7 vs 6.1 (zoledronic acid vs placebo)
								15.1 vs 8.1 (patients BM-
Hendriks, 2014	186	64 (34,4%)	162	nd	CT vs TKI (119 vs 48)	nd	nd	15.5 vs 9.0 vs 3.2 (EGFR+ vs KRAS+ vs WT)
Murakami , 2014	100	100 (100%)	77	12	Docetaxel (after one or two prior line of CT)	Zoledronic acid	2.7 vs 2.6 (docetaxel+zoledronic acid vs docetaxel)	10.4 vs 9.7 (docetaxel+zoledronic acid vs docetaxel)
Huang , 2015	114	62 (54,4%)	62	0	TKI	Biphosphonates	15.0 vs 7.3 (TKI+biphosponates vs TKI)	25.2 vs 10.4 (TKI+biphosponates vs TKI)
Rihimaki, 2014	9830	3342	6094	4030	nd	nd	nd	5
Huang , 2015	114	62 (54,4%)	62	0	TKI	Biphosphonates	15.0 vs 7.3 (TKI+biphosponates vs TKI)	25.2 vs 10.4 (TKI+biphosponates vs TKI)
Santini, 2015	2003	661 (33%)	436	nd	CT vs TKI (564 vs 199)	Biphosphonates	nd	9.5
Chen, 2016	1510	234 (15,5%)	292	nd	nd	nd	nd	10.5
Zhang, 2017	2975	1560 (52,4%)	552	nd	CT	Biphosphonates	5.5 vs 5.6 (CT+biphosphonates vs CT)	13.7 vs 13.6 (CT+biphosphonates vs CT)

THE ERA OF TARGET THERAPY

Bone metastases in EGFR+ NSCLC

Lung Cancer 84 (2014) 86–91

Contents lists available at ScienceDirect

Lung Cancer

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

EGFR mutated non-small cell lung cancer patients: More prone to development of bone and brain metastases?

L.E.L. Hendriks[a,*], E.F. Smit[b], B.A.H. Vosse[a], W.W. Mellema[b], D.A.M. Heideman[c], G.P. Bootsma[d], M. Westenend[e], C. Pitz[f], G.J. de Vries[g], R. Houben[h], K. Grünberg[c], M. Bendek[i], E.-J.M. Speel[i], A.-M.C. Dingemans[a]

THE ERA OF TARGET THERAPY

Bone metastases in EGFR+ NSCLC

Mutation status and bone/brain metastases.

	EGFR+ N = 62	KRAS+ N = 65	Wildtype N = 62	p-Value
Bone metastases				
Imaging at 1st diagnosis of mNSCLC N (%)				
PET-CT	38 (61.3)	46 (70.8)	48 (77.4)	0.232
CT[a]	17 (27.4)	13 (20.0)	11 (17.7)	
Bone scintigraphy[b]	5 (8.1)	4 (6.2)	2 (3.3)	
Missing	2 (3.2)	2 (3.0)	1 (1.6)	
Bone mets N (%)				
Yes	37 (59.7)	34 (52.3)	31 (50.0)	0.528
At diagnosis	20 (54.1)	26 (76.5)	18 (58.1)	0.121
During follow up	17 (45.9)	8 (23.5)	13 (41.9)	
No	25 (40.3)	31 (47.7)	31 (50.0)	
Time to bone mets months [SD]	13.4 [±10.6]	23.3 [±19.4]	16.4 [±9.6]	0.201
SRE+ N (%)	19 (51.4)	22 (64.7)	15 (48.4)	0.361
Time to 1st SRE months [95% CI]	12.9 [5.0–20.7]	7.3 [0.0–14.9]	3.5 [0–7.7]	0.213
Post bone mets survival months [95% CI]	15.5 [10.6–20.3]	9.0 [5.2–12.9]	3.2 [0–6.9]	EGFR/KRAS 0.049 EGFR/WT 0.004

SRE+ N (%)	19 (51.4)	22 (64.7)	15 (48.4)	0.361
Time to 1st SRE months [95% CI]	12.9 [5.0–20.7]	7.3 [0.0–14.9]	3.5 [0–7.7]	0.213
Post bone mets survival months [95% CI]	15.5 [10.6–20.3]	9.0 [5.2–12.9]	3.2 [0–6.9]	EGFR/KRAS 0.049 EGFR/WT 0.004

EGFR: epidermal growth factor receptor; 95% CI = 95% confidence interval; SD = standard deviation; SRE = skeletal related event; EGFR-TKI = epidermal growth factor receptor; WBRT = whole brain radiotherapy; SRS = stereotactic radiosurgery.

[a] Ct-thorax/upper abdomen.

[b] When both PET-CT and bone scintigraphy were performed, patients were scored for "PET-CT".

[c] Only low dose CT brain during PET-CT was scored as "none".

Hendriks L.E.L. Lung Cancer 2014

THE ERA OF TARGET THERAPY

Bone metastases in EGFR+ NSCLC

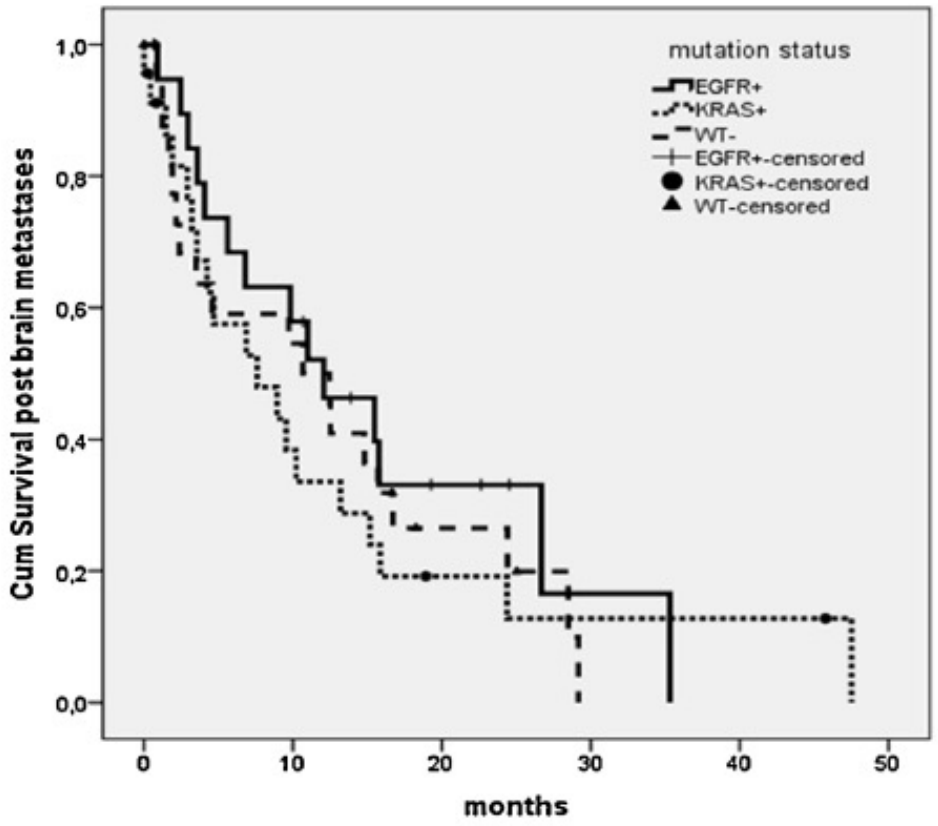


Fig. 2. survival post brain metastases for EGFR+, KRAS+ and WT patients.

5. Conclusion

Incidence of metastatic bone disease and brain metastases was not different between EGFR+, KRAS+ and WT patients. Furthermore, survival post metastatic bone disease was significantly longer in the EGFR+ group, which stresses the impact of bone management especially in these patients and probably warrant more intense screening for metastatic bone disease.

Hendriks L.E.L. Lung Cancer 2014

THE ERA OF TARGET THERAPY

Bone metastases in EGFR+ NSCLC

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 41

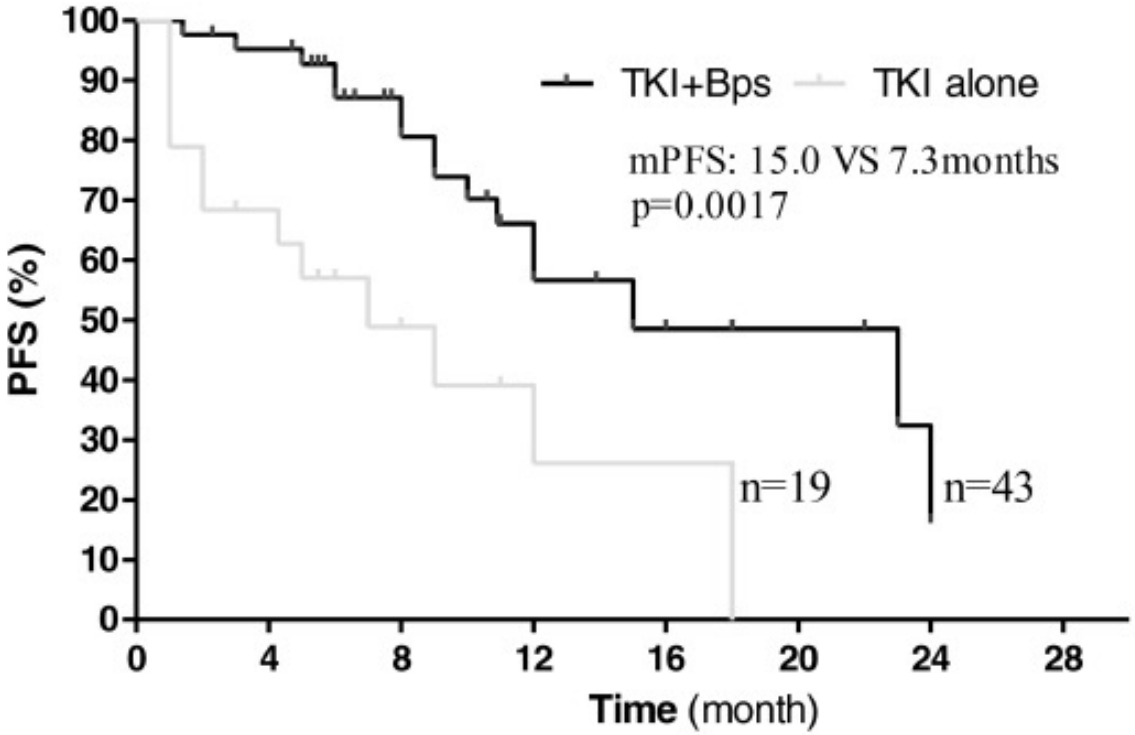
Research Paper

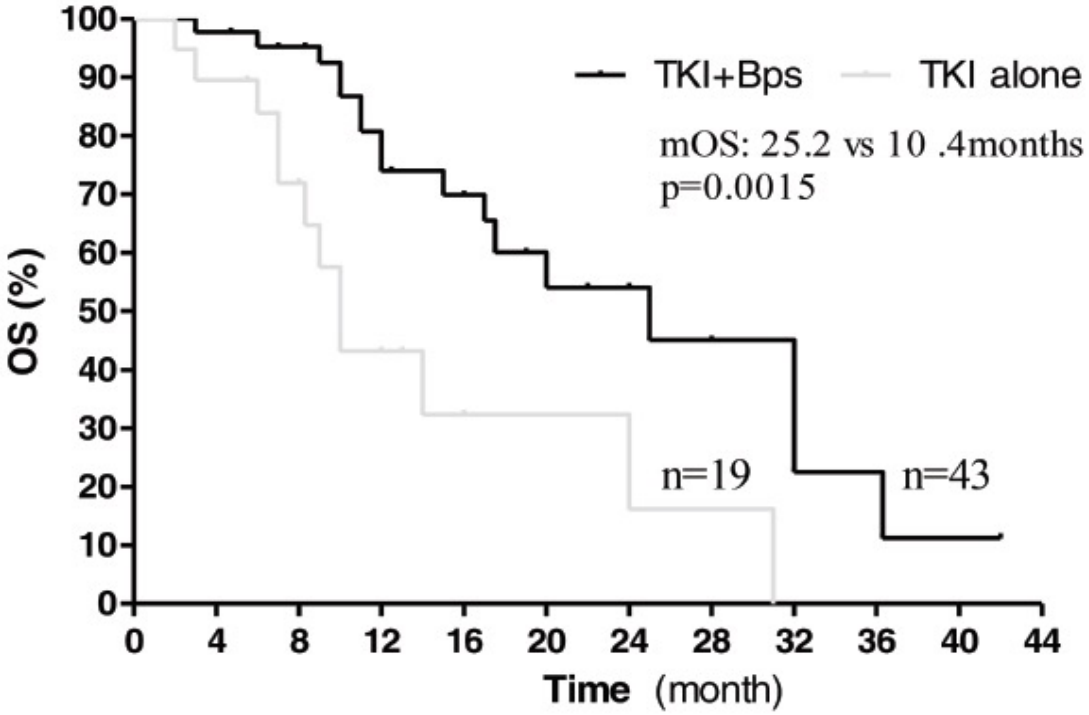
Bisphosphonates enhance EGFR-TKIs efficacy in advanced NSCLC patients with EGFR activating mutation: A retrospective study

Chu-Ying Huang[1,3,*], Li Wang[1,4,*], Cheng-Jun Feng[1,*], Ping Yu[2,*], Xiao-Hong Cai[2], Wen-Xiu Yao[2], Yong Xu[1], Xiao-Ke Liu[1], Wen-Jiang Zhu[1], Yan Wang[1,5], Jin Zhou[2], You Lu[1], Yong-Sheng Wang[1]

THE ERA OF TARGET THERAPY

Bone metastases in EGFR+ NSCLC





Conclusions: Concomitant use of bisphosphonates and EGFR-TKIs improves therapeutic efficacy and brings survival benefits to NSCLC patients with EGFR mutation and bone metastases.

Huang C.Y., Oncotarget. 2015

THE ERA OF TARGET THERAPY

Bone metastases in EGFR+ NSCLC

SCIENTIFIC REPORTS

OPEN

Natural History of Non-Small-Cell Lung Cancer with Bone Metastases

Santini Daniele[1], Barni Sandro[2], Intagliata Salvatore[1], Falcone Alfredo[3], Ferraù Francesco[4], Galetta Domenico[5], Moscetti Luca[6], La Verde Nicla[7], Ibrahim Toni[8], Petrelli Fausto[2], Vasile Enrico[3], Ginocchi Laura[3], Ottaviani Davide[9], Longo Flavia[10], Ortega Cinzia[11], Russo Antonio[12], Badalamenti Giuseppe[12], Collovà Elena[13], Lanzetta Gaetano[14], Mansueto Giovanni[15], Adamo Vincenzo[16], De Marinis Filippo[17], Satolli Maria Antonietta[18], Cantile Flavia[19], Mancuso Andrea[20], Tanca Francesca Maria[21], Addeo Raffaele[22], Russano Marco[1], M Sterpi[1], Pantano Francesco[1], Vincenzi Bruno[1] & Tonini Giuseppe[1]

Received: 13 July 2015
Accepted: 18 November 2015
Published: 22 December 2015

Egfr Mutation	
Unknown	70,5% (459)
Known	29,5% (195)
Wild Type	74,9% (146)
Mutated	25,1% (49)

THE ERA OF TARGET THERAPY

Bone metastases in EGFR+ NSCLC

- 57.5% bone M+ at diagnosis
- 57.7% SRE

- **9 months** = time to bone M+
- **6 months** = time to first SRE

- **9.5 m** =OS after bone M+ diagnosis
- **7 m** = OS after the first SRE

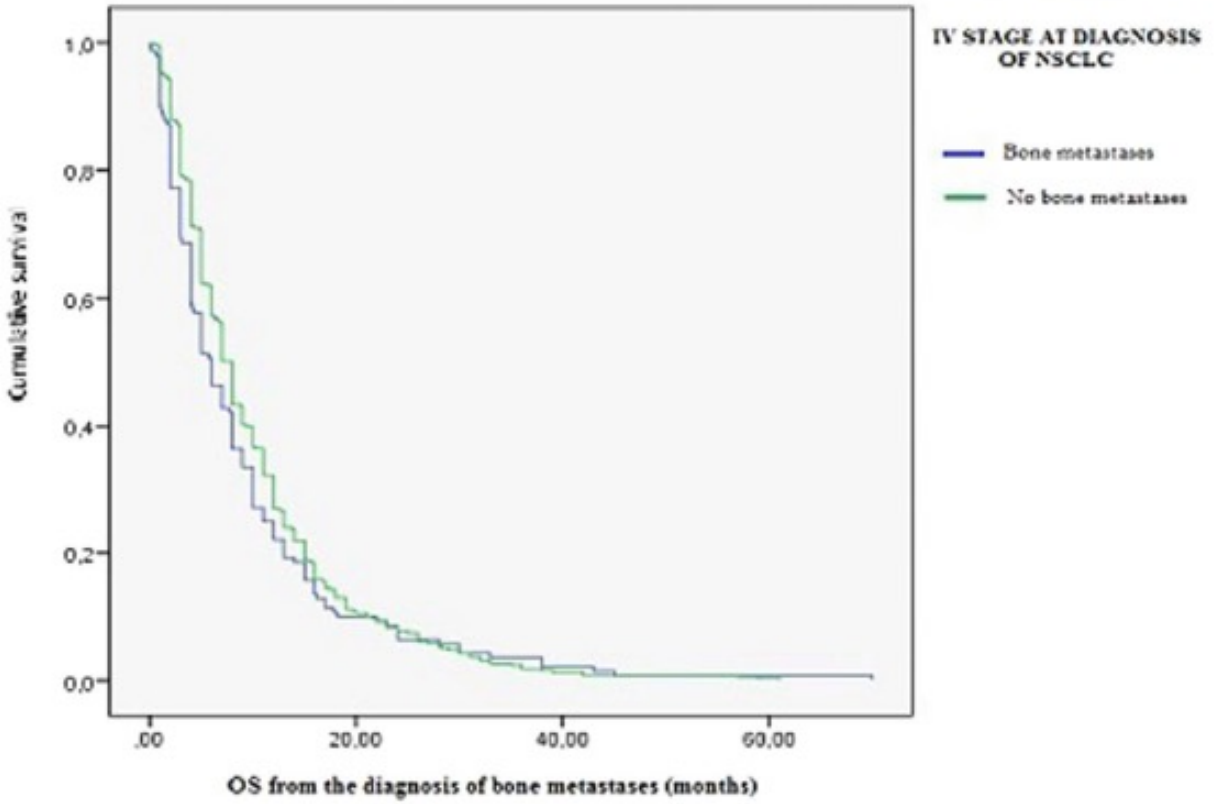
- **6 m** = OS if SRE as onset of bone M+
- **10 m** = OS if SRE after diagnosis of bones M+

SREs	First SRE	Second SRE	Third and subsequent SREs
Radiotherapy	71.4% (262)	79.2% (76)	61.9% (13)
Pathologic fractures	16.3% (60)	9.4% (9)	19% (4)
Spinal cord compression	6% (22)	2.1% (2)	9.5% (2)
Hypercalcemia	4.1% (15)	4.2% (4)	9.5% (2)
Surgery	3.3% (12)	5.2% (5)	14.3% (3)

Santini D. Sci. Rep. 2015

THE ERA OF TARGET THERAPY

Bone metastases in EGFR+ NSCLC



"The selective evaluation of patients with stage IV at diagnosis of NSCLC has **NOT** shown **statistically significant differences in OS** between **patients with bone metastases and patients without bone metastases at diagnosis**."

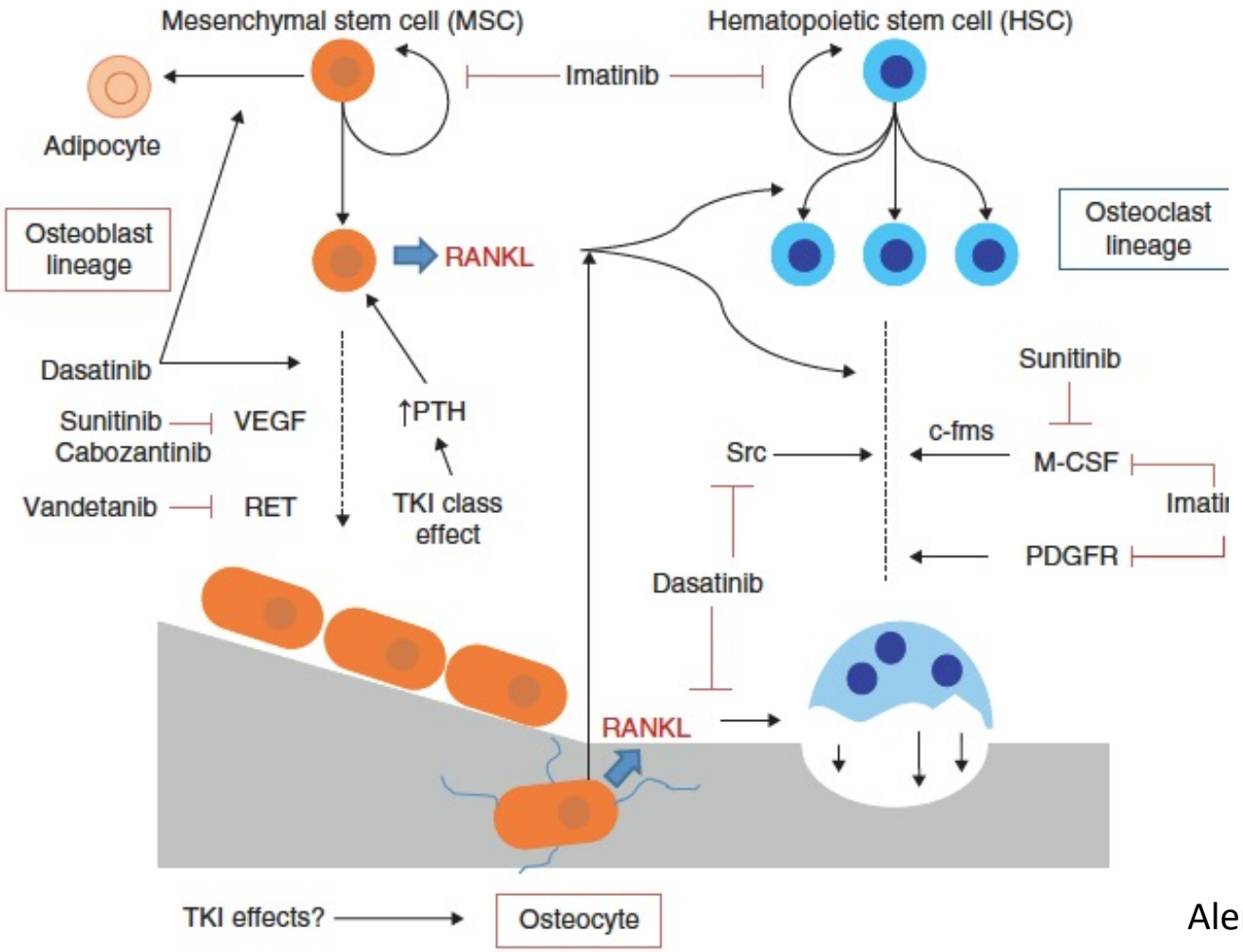
"**Not even** the **time to the onset of bone metastases** appears to be a **factor able to predict differences in overall survival from diagnosis of bone metastases**"

Figure 1. IV stage at diagnosis: patients with or without bone metastases. Kaplan-Meier survival analysis.

Santini D. Sci. Rep. 2015

THE ERA OF TARGET THERAPY

Effects of TKIs on osteoblast and osteoclast lineages



Aleman, Endocr Relat Cancer. 2014

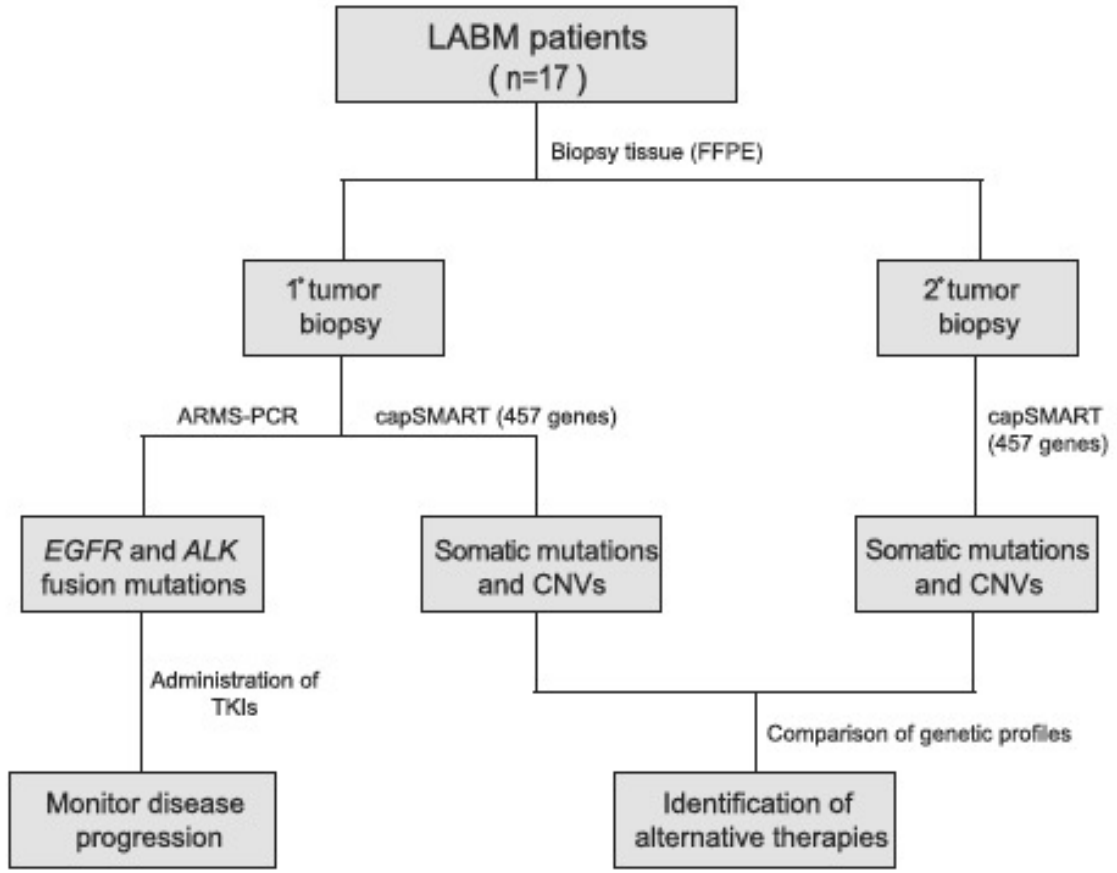
FUTURE IN THE ERA OF TARGET THERAPY

RESEARCH ARTICLE Open Access

Genetic profiling of primary and secondary tumors from patients with lung adenocarcinoma and bone metastases reveals targeted therapy options

- Currently, for **LABM patients**, there is a paucity of information on the **key genetic changes** present in the **primary tumor** and clonal variants that manifest as **metastases**

- **Detailed genetic profiling of the primary tumors and secondary metastases** showed that while the clonal metastases **closely mimicked the genetic changes in the primary tumor**, **new driver** and **passenger oncogenic mutations** as well as **copy number variations** can arise



Personalized targeted therapy options effective against both the primary tumor and secondary metastases

Huang L., et al. Molecular Medicine 2020

FUTURE IN THE ERA OF TARGET THERAPY

Genetic profiling of primary and secondary tumors from patients with lung adenocarcinoma and bone metastases reveals targeted therapy options

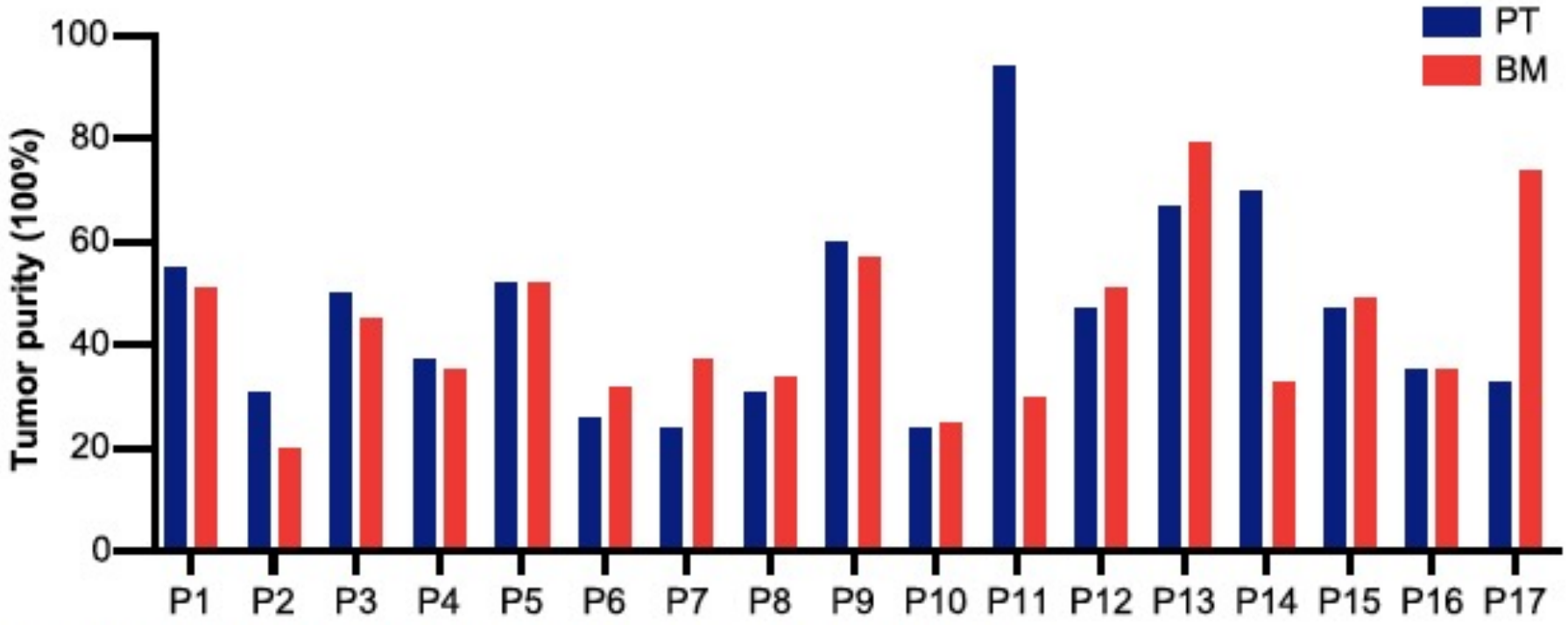


Fig. 2 Tumor purity by histology. Purity was defined as the ratio of tumor to normal cells

Huang L., et al. Molecular Medicine 2020

FUTURE IN THE ERA OF TARGET THERAPY

RESEARCH ARTICLE Open Access

Genetic profiling of primary and secondary tumors from patients with lung adenocarcinoma and bone metastases reveals targeted therapy options

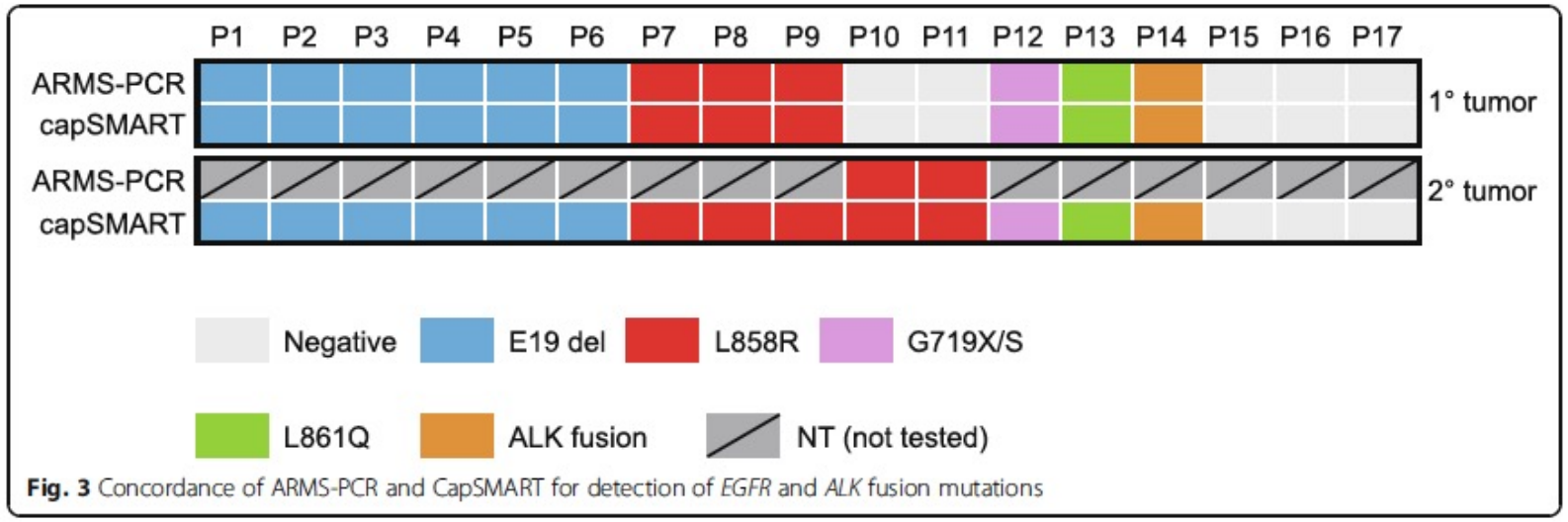
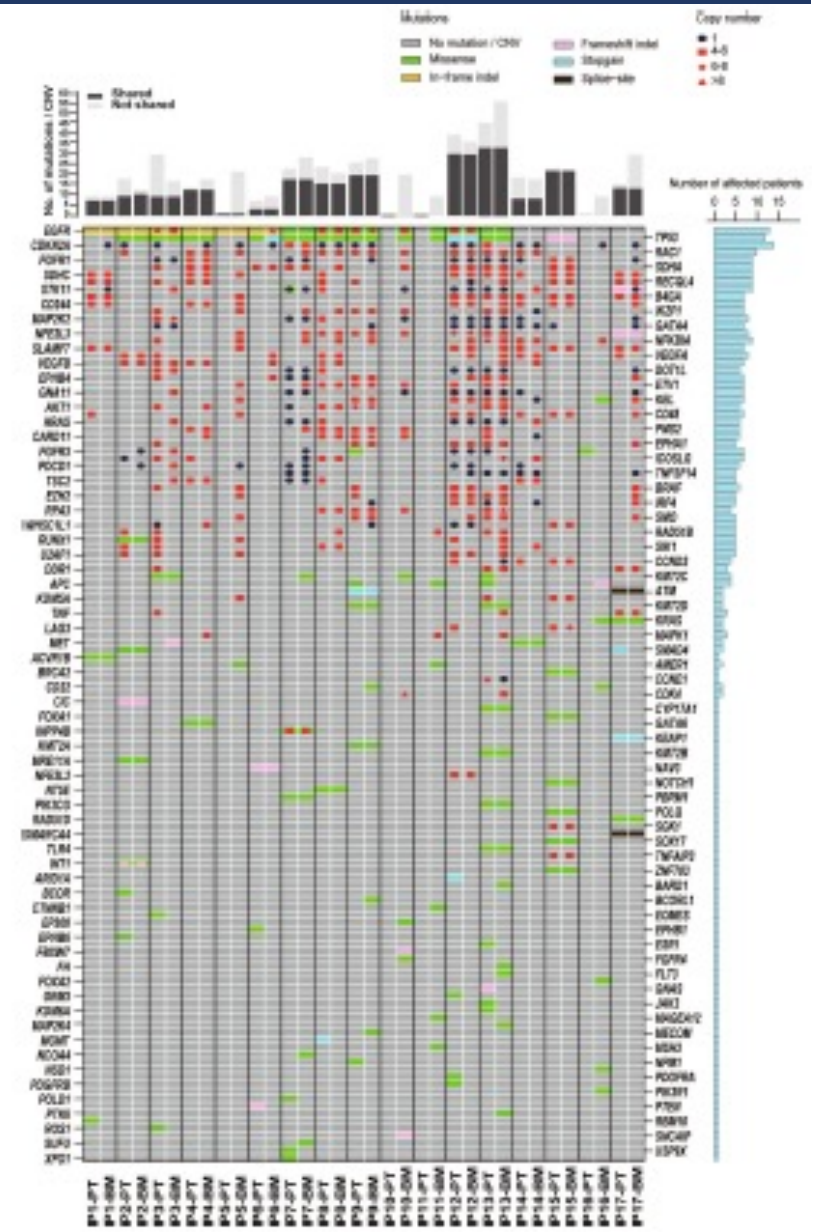


Fig. 3 Concordance of ARMS-PCR and CapSMART for detection of *EGFR* and *ALK* fusion mutations



Huang L., et al. Molecular Medicine 2020

FUTURE IN THE ERA OF TARGET THERAPY

Genetic profiling of primary and secondary tumors from patients with lung adenocarcinoma and bone metastases reveals targeted therapy options

«…the **new standard of care** should
involve an **initial comprehensive screen of the PT biopsy**
together with any available BMs that are accessible for biopsy.

This approach will ensure that the treating clinician
is provided with **more personalized genetic information**
to **tailor effective targeted therapy options** and
develop a **more effective treatment regimen**…»

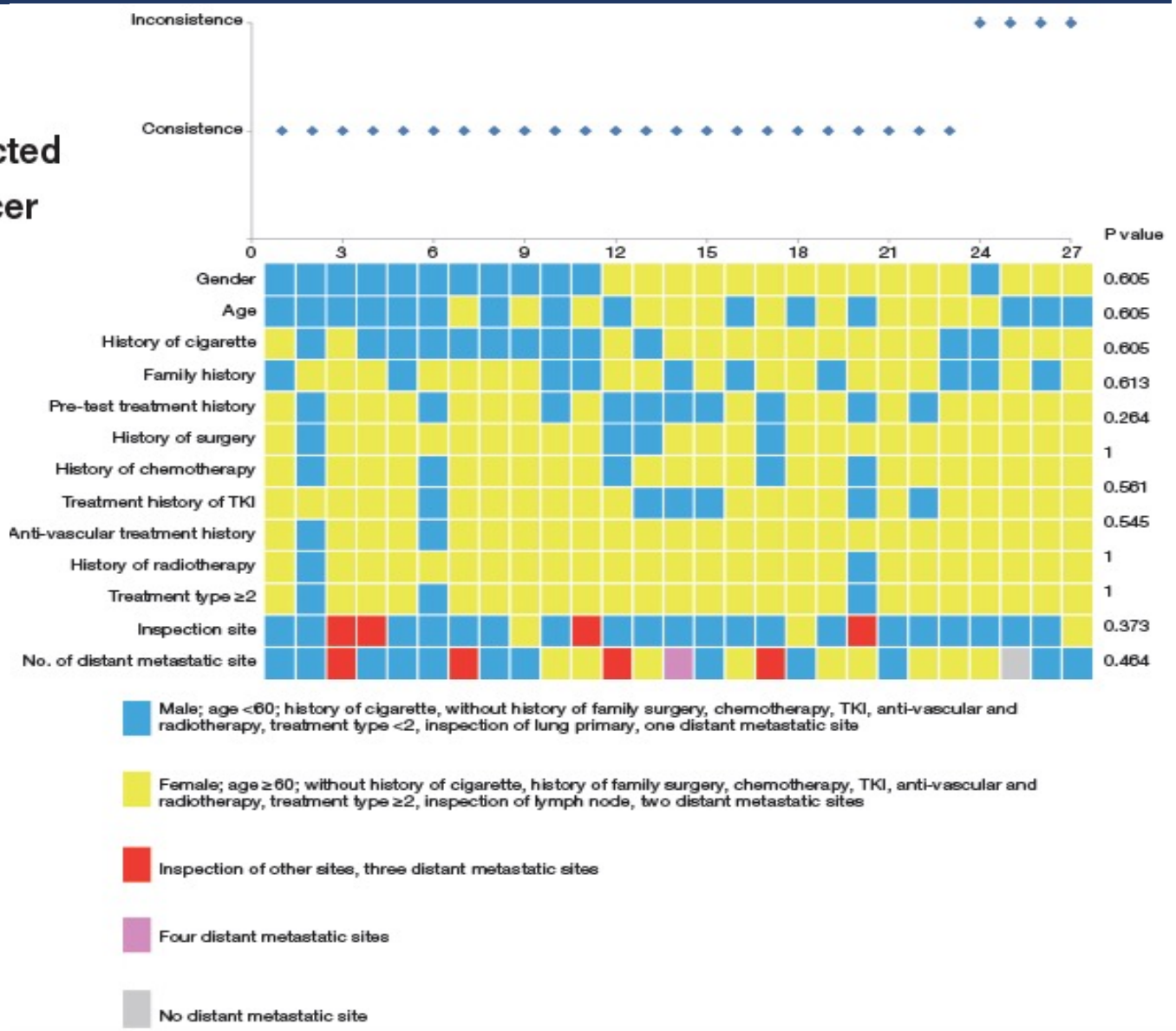
Huang L., et al. Molecular Medicine 2020

FUTURE IN THE ERA OF TARGET THERAPY

Original Article

Consistency of genotyping data from simultaneously collected plasma circulating tumor DNA and tumor-DNA in lung cancer patients

- The overall sequencing driver genes in plasma samples relative to tumor samples:
  - ✓ 85,2% concordance
  - ✓ 87.0% sensitivity
  - ✓ 75% specificity



The comparison of clinical characteristics of consistent and inconsistent patients.

Zhang J., Journal of Thoracic Disease 2020

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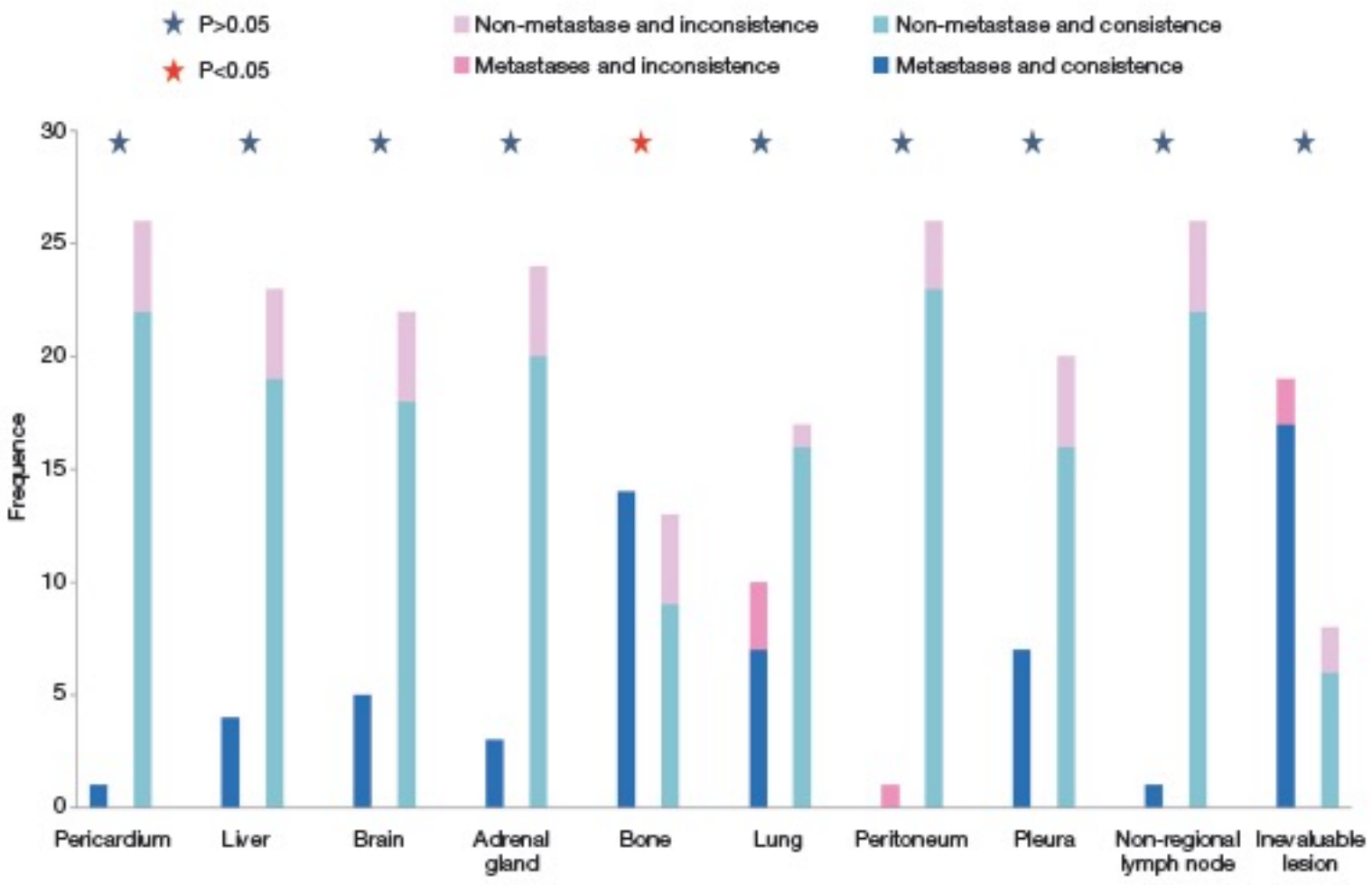


The relationship between consistency and distant metastases sites.

- Concordance:
- 100% in patients with bone metastases
- 69.2% without bone metastases

Zhang J., Journal of Thoracic Disease 2020

FUTURE IN THE ERA OF TARGET THERAPY

Original Article

Consistency of genotyping data from simultaneously collected plasma circulating tumor DNA and tumor-DNA in lung cancer patients

Patients with bone metastases = greater accuracy for tissue and plasma

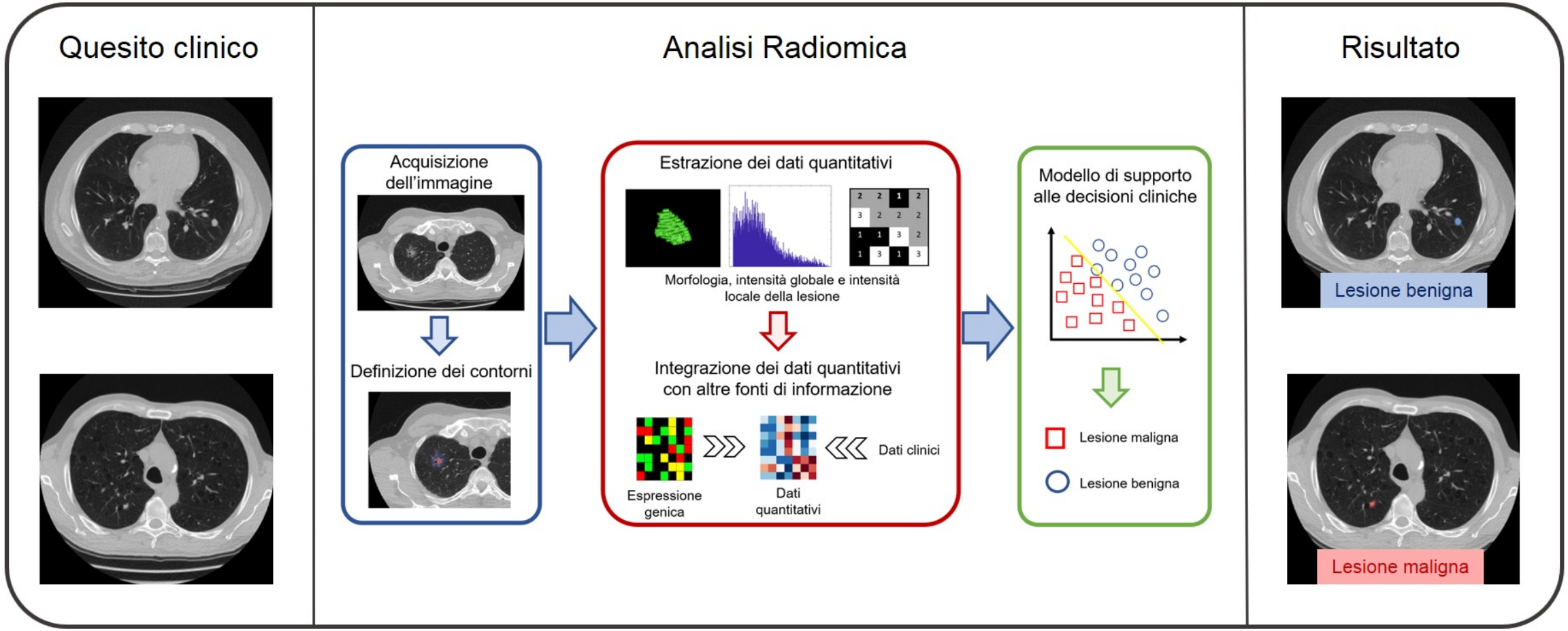
- Greater tumor burden and advanced tumor stage
  → usually accompanied by bone metastases
  → promising predictors of higher sensitivity

ctDNA was able to identify
75% of the identical information in driver genes,
with higher rates of concordance in lung cancer patients with
bone metastases or *TP53* mutation-positive plasma samples.

Zhang J., Journal of Thoracic Disease 2020

FUTURE IN THE ERA OF TARGET THERAPY

RADIOMICA



FUTURE IN THE ERA OF TARGET THERAPY

cancers

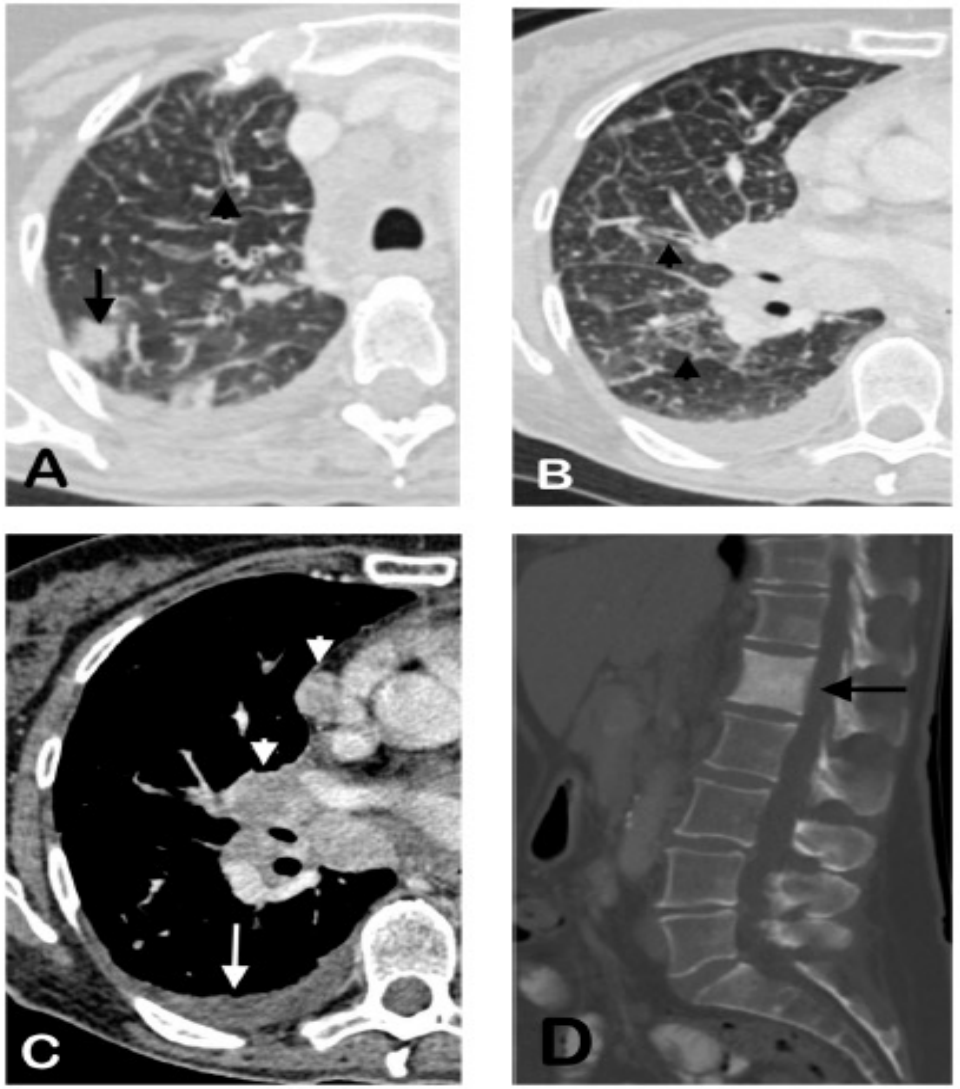
MDPI

Article

Imaging Features and Patterns of Metastasis in Non-Small Cell Lung Cancer with *RET* Rearrangements

Representative imaging features of RET+ NSCLC

- **A arrow:** solid nodule in the peripheral right upper lobe
- **A,B arrow:** lymphangitic carcinomatosis
- **C arrow:** malignant pleural eusion
- **C arrowheads:** mediastinal and hilar lymphadenopathy
- **D arrow:** sclerotic osseous metastasis of the first lumbar vertebral body



Digumarthy S.R., et al. Clinical Lung Cancer 2020

FUTURE IN THE ERA OF TARGET THERAPY

cancers

MDPI

Article

Imaging Features and Patterns of Metastasis in Non-Small Cell Lung Cancer with *RET* Rearrangements

RET+ NSCLC shares several radiologic features with ALK+ and ROS1+ NSCLC

- solid density of the primary tumor
- high frequencies of lymphangitic carcinomatosis
- pleural, brain, and bone metastases

Bone metastases = sclerotic in nature

Metastatic Site	*RET* (N = 22)	*ALK* (N = 87)	*ROS1* (N = 49)	*RET* vs. *ALK* *p*-Value	*RET* vs. *ROS1* *p*-Value
Intrathoracic	14 (64%)	64 (74%)	41 (84%)	0.429	0.074
Lung	4 (18%)	18 (21%)	18 (37%)	1.000	0.167
Pleural	10 (45%)	35 (40%)	20 (41%)	0.809	0.797
Lymphangitic carcinomatosis	6 (27%)	35 (40%)	21 (43%)	0.329	0.292
Pericardium	1 (5%)	2 (2%)	2 (4%)	0.495	1.000
Extrathoracic	17 (77%)	65 (75%)	29 (59%)	1.000	0.183
Bone	10 (45%)	41 (47%)	16 (33%)	1.000	0.425
Sclerotic metastasis	8 (80%)	28 (68%)	9 (56%)	0.703	0.399
Liver	3 (14%)	21 (24%)	10 (20%)	0.393	0.741
Brain	7 (32%)	22 (25%)	5 (10%)	0.592	*0.039*
Distant lymph nodes	5 (23%)	17 (20%)	8 (16%)	0.769	0.524
Adrenal	4 (18%)	6 (7%)	7 (14%)	0.114	0.729
Soft tissue	1 (5%)	5 (6%)	1 (2%)	1.000	0.527

Digumarthy S.R., et al. Clinical Lung Cancer 2020

FUTURE IN THE ERA OF TARGET THERAPY

Original Study

Computed Tomography Imaging Features and Distribution of Metastases in *ROS1*-rearranged Non–Small-cell Lung Cancer

Supplemental Table 1 Primary Tumor Imaging Features (n = 251)

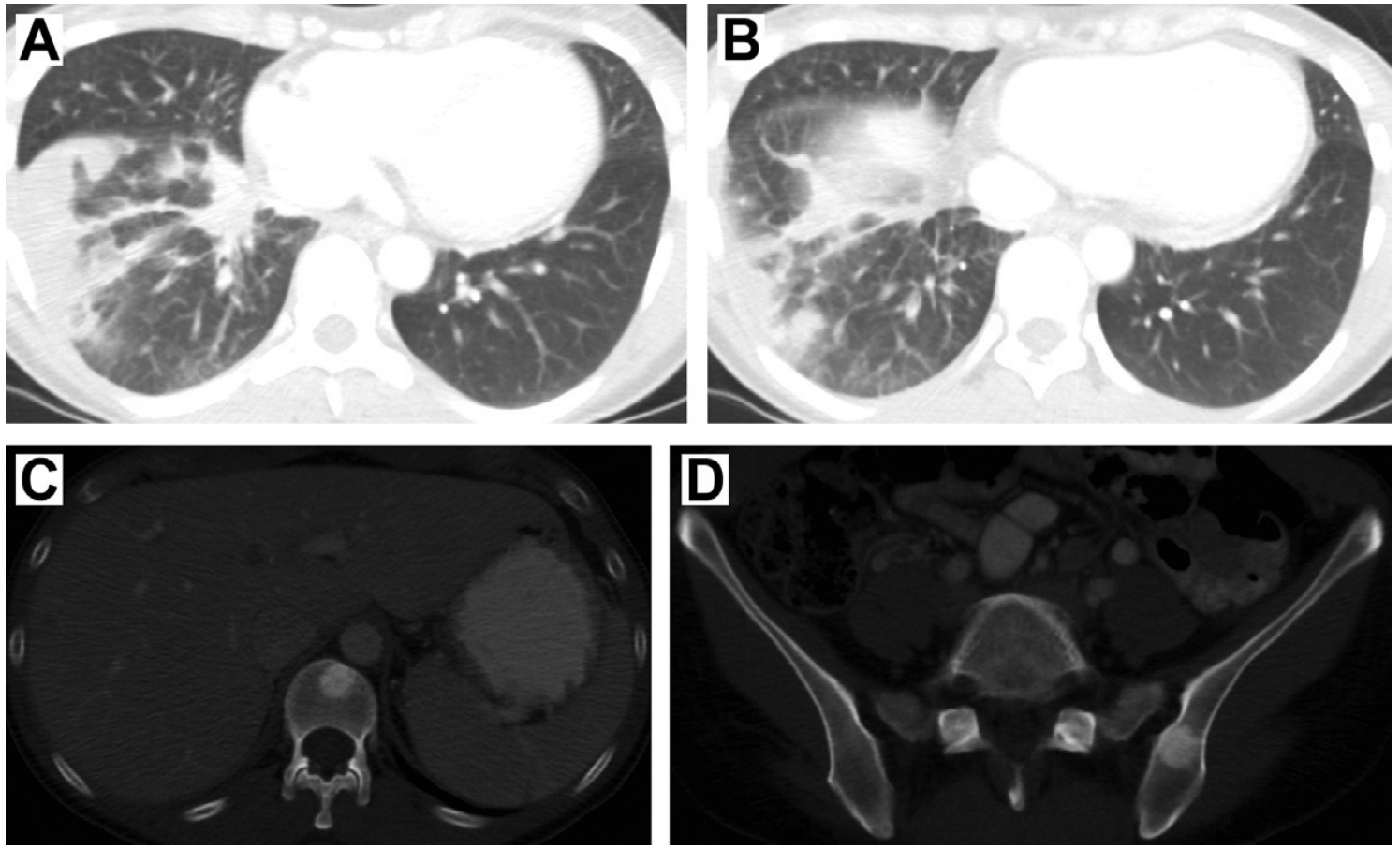
Primary Tumor Features	All (n = 251)	Mutation			*P* Value	
		ROS1 (n = 48)	*ALK* (n = 86)	*EGFR* (n = 117)	*ROS1* vs. *ALK*	*ROS1* vs. *EGFR*
Bone					.05	.17
Yes	106 (41)	16 (30)	41 (47)	49 (42)		
No	151 (59)	37 (70)	46 (53)	68 (58)		
Bone metastasis type					.10	<.01
None	151 (59)	37 (70)	46 (53)	68 (58)		
Lytic	62 (24)	7 (13)	13 (15)	42 (36)		

Digumarthy S.R., et al. Clinical Lung Cancer 2020

FUTURE IN THE ERA OF TARGET THERAPY

Computed Tomography Imaging Features and Distribution of Metastases

in ROS1-rearranged Non–Small-cell Lung Cancer



ROS1-rearranged Lung Adenocarcinoma and
Sclerotic Osseous Metastases ((C) Spine and (D) Left Iliac Bone)

The most common sites of metastasis in **ROS1-rearranged NSCLC** in our cohort were the lungs (42%), pleura (40%), and **bones (30%).**

Sclerotic (or osteoblastic) bone metastases were more common in ROS1- rearranged and ALK rearranged NSCLC compared with EGFR mutant NSCLC.

Digumarthy S.R., et al. Clinical Lung Cancer 2020

FUTURE IN THE ERA OF TARGET THERAPY

Real-world treatment patterns and outcomes in patients (pts) with advanced, ALK+ non-small cell lung cancer (NSCLC) in Europe

Table: 1340P

Baseline characteristics	Alectinib (N=70)	Crizotinib (N=229)
Median Age	62	63
Female Sex (%)	40%	46%
Overall median ToT in days (d)	360 d	470 d
CNS metastasis at diagnosis (%;median ToT)	21% (454 days)	14% (518 d)
Site of metastatic progression after first-line		
CNS (%; median ToT)	13% (243 d)	30% (455 d)
Visceral (%; median ToT)	66% (394 d)	48% (441 d)
Bone (%; median ToT)	30% (365 d)	27% (319 d)

Stoyanov N., Annals of Oncology 2020

From Literature to Real Life

Osteoblastic (or sclerotic)

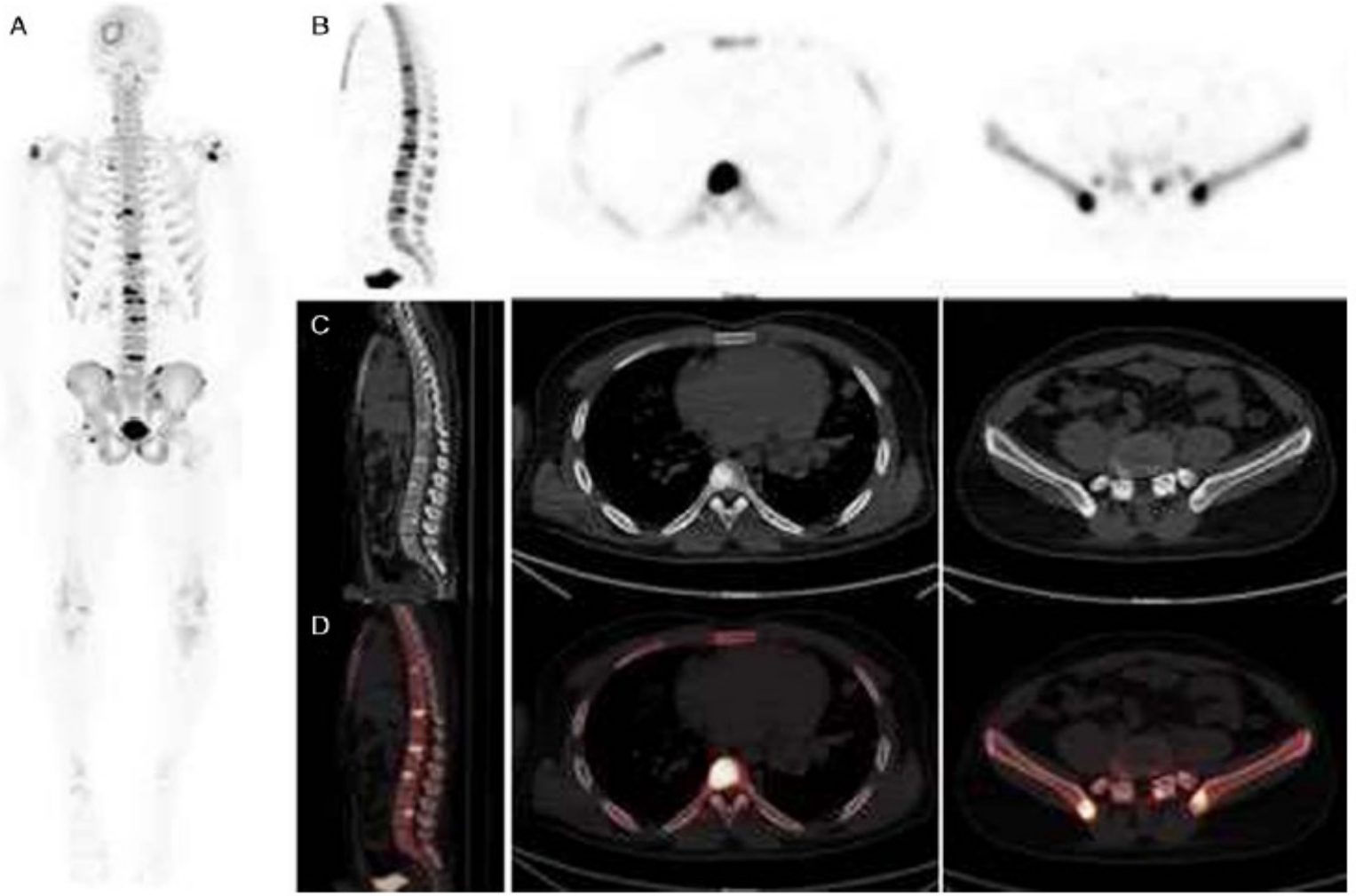
- **Deposition** of new bone
- Prostate cancer, carcinoid, SCLC, HL or medulloblastoma
- **New bone formation is not necessarily preceded by bone resorption**
- Transforming growth factor, bone morphogenic proteins (BMP) and endothelin-1 are associated with osteoblast generation.
- PSA, can cleave PTHrP, allowing the osteoblastic reaction predominate by decreasing bone reabsorption
- Runx-2 → osteoblast differentiation

Iwamura M, *Urology*1996
Yang X, *Trends Mol Med* 2002
Coleman R, *Semin Oncol* 2001

THE REAL LIFE IN THE ERA OF TARGET THERAPY

Clinical case

- 18-year-old man
- NSCL with rearrangement of ALK gene at chromosome 2p23
- Stage IV with brain and bone metastatic
- Alectinib as first line of treatment



Usmani S. Clinical Nuclear Medicine 2018

THE REAL LIFE IN THE ERA OF TARGET THERAPY

Clinical case

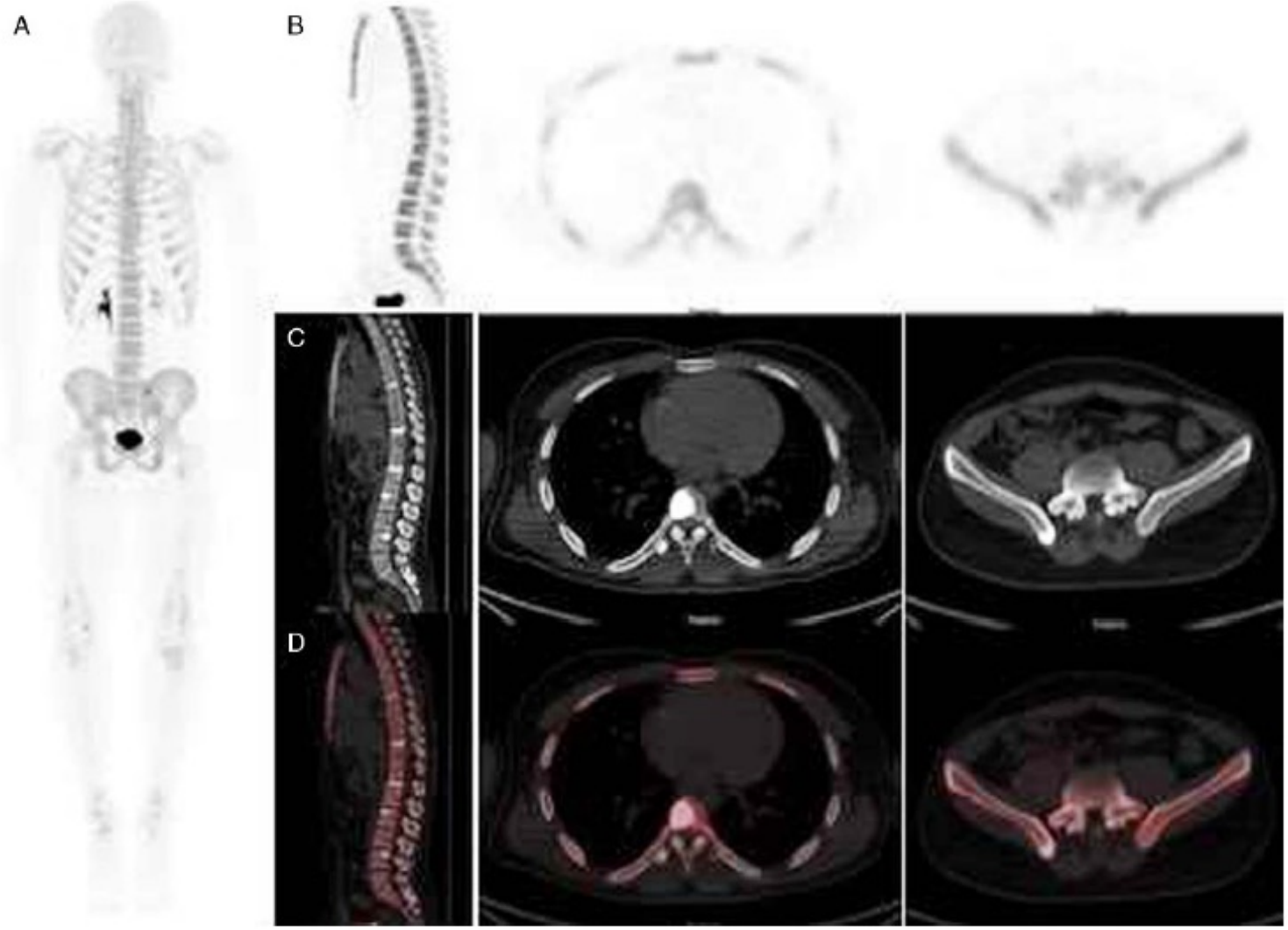
- 8 months of treatment with alectinib
- **Resolution of bone lesions**

The present case show

rapid and good response to alectinib

in metastatic ALK-positive

non–small cell lung carcinoma



Usmani S. Clinical Nuclear Medicine 2018

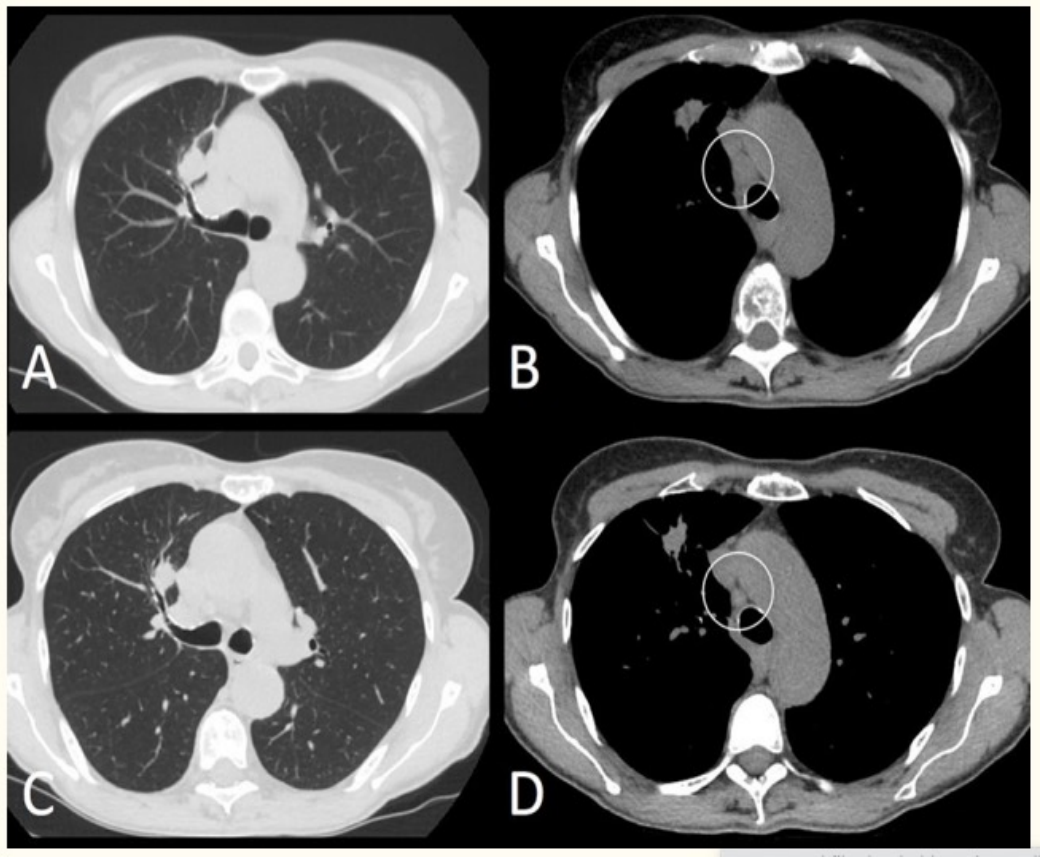
THE REAL LIFE IN THE ERA OF TARGET THERAPY

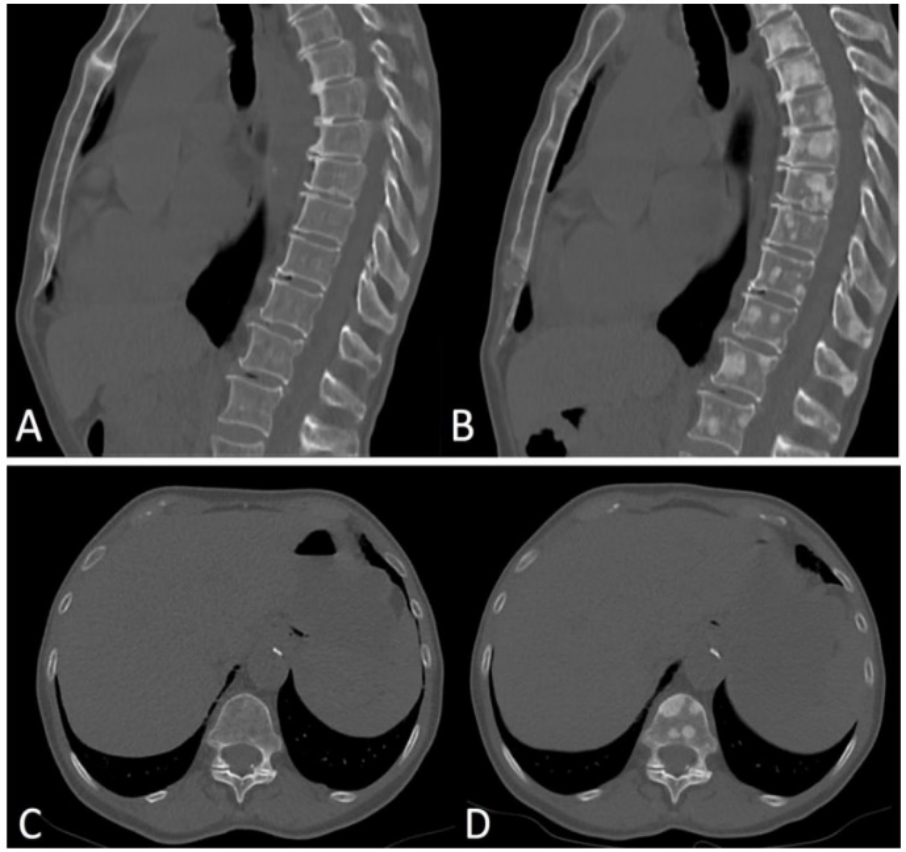
Clinical case

- 72-year-old female never-smoker
- stage IV EGFR+ lung ADK
- primary lesion: right upper lobe, 2.9 cm greatest diameter
- TNM: cT1bN3M1b: hilar, mediastinal and supraclavicular lymph nodes and distant metastases in liver
- This patient was started on first line TKI and seemingly developed new bone metastases under this treatment

THE REAL LIFE IN THE ERA OF TARGET THERAPY

Clinical case





Numerous new blastic bone lesions in the spine, ribs and sternum…

Misinterpretation of these findings as new metastases would classify this patient as progressive cancer disease

J Belg Soc Radiol. 2020

THE REAL LIFE IN THE ERA OF TARGET THERAPY

Clinical case

- As there was a remarkable **discrepancy between the partial response seen in the primary tumor** and non-osseous metastatic locations, the possibility of a **bone flare phenomenon** was considered…
- In this case report, we demonstrate that **new bony lesions are not always synonymous with disease progression**…

THE REAL LIFE IN THE ERA OF TARGET THERAPY

- **Osteoblastic bone flaring** is a phenomenon whereby new or more prominent osteoblastic bony lesions arise in the presence of a **clear therapeutic response** in other tumor sites
  - Caused by **increased osteoblastic activity**
  - Representing **healing of the bone metastases**
  - Sign of **therapeutic efficacy**
  - **Mechanism** of osteoblastic flaring
    - direct effect of the EGFR TKI on bone metabolism
    - innate healing reaction upon reaching SD/PR by successful treatment

Normanno N, Endocr Relat Cancer. 2005
Suzuki M, Clinical Cancer Research: 2007
Emami KH, Cancer Lett. 2007

Pluquet, *J Thorac Oncol*. 2010
Lind JS, *J Thorac Oncol*. 2010

Chao HS, *Clin Nucl Med*. 2009
Gelsomino F, *J Thorac Oncol*. 2016

Osteoblastic ???

Not at all !!!

Osteolitic

- **Destruction** of normal bone
- Multiple myeloma (MM), renal cell carcinoma, melanoma, non-small cell lung cancer, non-hodgkin lymphoma, thyroid cancer or langerhans-cell histiocytosis
- **Bone destruction by osteoclasts or compression of vasculature → ischaemia**
- **PTHrP**: major role in the development of osteolytic lesions
- Bone **microenvironment** induces cancer cells to express PTHrP or cells that metastasize to bone have an intrinsic higher PTHrP expression?
- **RANKL**: a critical role in the formation of osteoclasts

Selvaggi G, *Clin Rev Oncol Hematol*2005
Taube T, *Bone* 1994
Southby J, *Cancer Res* 1990
Kohno N, *Surg Today* 1994
Dougall W, *Genes Dev* 1999

Osteoporosis

The **NSCLC** patient is often an **elderly** patient

Patients with **NSCLC EGFR+** are often **women**

Female and elderly patients
often suffer from **osteoporosis**

Osteoporotic lesions can often be confused with osteolytic metastatic lesions

ISTAT

*...si dichiara malato di **osteoporosi** il 4,7% della popolazione totale e il 17,5% delle persone con oltre sessantacinque anni...*

Osteolitic ???

Not always !!!

FUTURE IN THE ERA OF TARGET THERAPY

Bone metastases in NSCLC

- About 80% of patients with bone M+ will experience significant pain and a reduction of QoL
- SREs → pain, decreased quality of life, declines in physical, functional and emotional well being and negatively affect survival
- Over 60% of patients with BM will develop skeletal-related events (SREs)

- ✓ **Radiotherapy**
- ✓ **Bone surgery**
- ✓ **Pathological fractures**
- ✓ **Spinal cord compression**
- ✓ **Hypercalcemia**

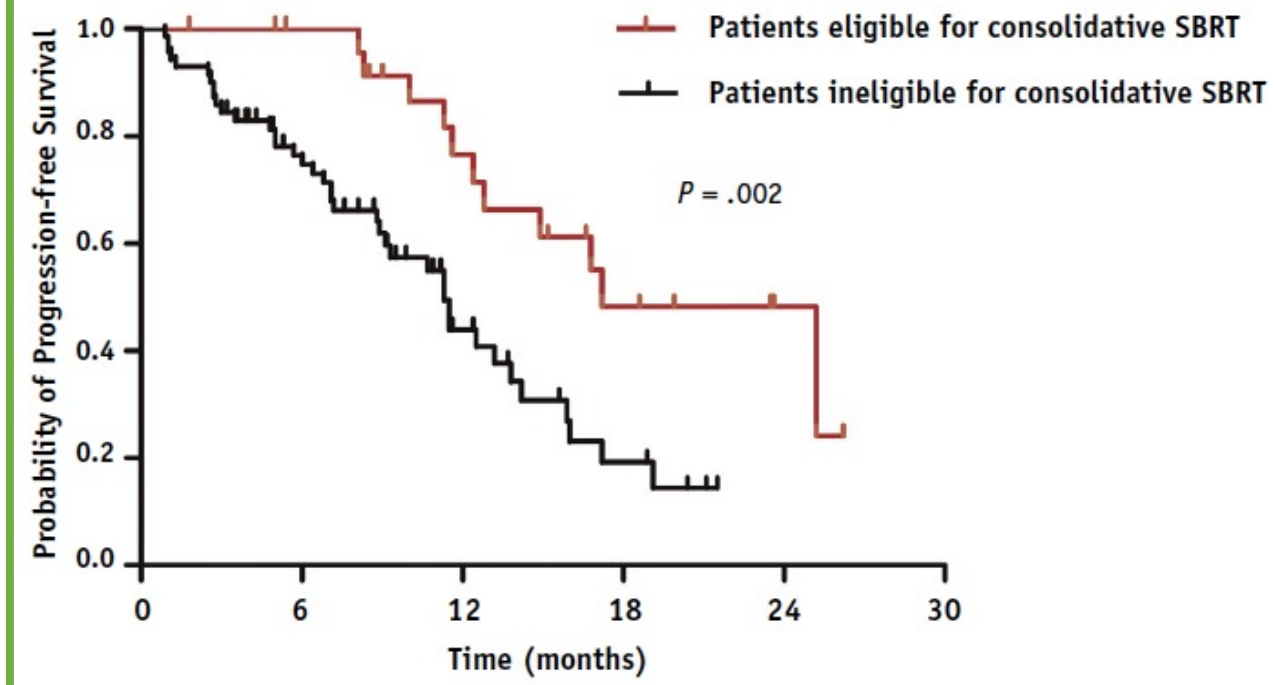
Kuchuk M, **et al;** *Lung Cancer*. 2015;89(2):197-202.

Oligoprogression and need for RT

Clinical Investigation

Pattern of Recurrence Analysis in Metastatic EGFR-Mutant NSCLC Treated with Osimertinib: Implications for Consolidative Stereotactic Body Radiation Therapy

International Journal of Radiation Oncology biology • physics
www.redjournal.org



The majority of osimertinib-treated patients developed PD within the persistent lesions in initially involved sites. Patients with stage T1-2 before initiating osimertinib were particularly likely to become candidates for consolidative SBRT. The addition of SBRT to residual sites of disease at maximal osimertinib response may prolong time to progression in subsets of patients with an oligoresidual disease state.

Guo et al, Int J Radiation Oncol Biol 2020

Oligoprogression and need for RT

Lung Cancer 130 (2019) 149–155

Contents lists available at ScienceDirect

Lung Cancer

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

Patterns of progression on osimertinib in EGFR T790M positive NSCLC: A Swiss cohort study

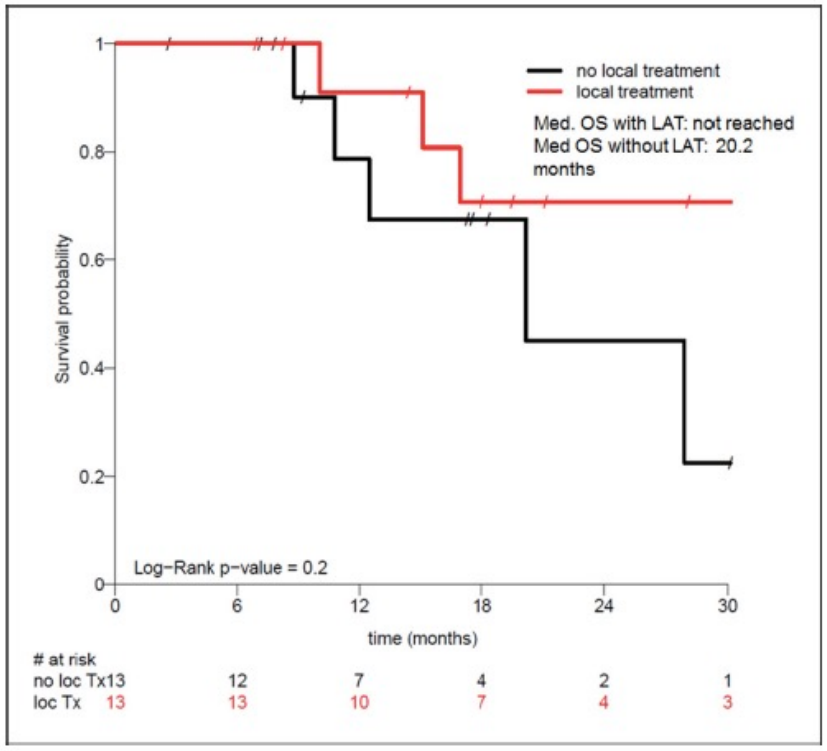


Fig. 2. OS in oligo-PD with/without LAT.

In patients with acquired osimertinib resistance, we observed a high rate (73%) of oligo-PD. Although OS of patients with oligo- versus systemic PD were similar, outcomes of patients with oligo-PD who received local ablative therapy were favorable with the majority continuing osimertinib for an extended period of time in addition to local therapy, supporting the concept of continuing osimertinib beyond progression in combination with LAT of progressing lesions. Prospective trials to confirm the role of LAT in patients with oligo-PD on osimertinib are warranted and currently ongoing (ETOP HALT). Patients with previous CNS metastases may benefit from regular radiological monitoring for progression.

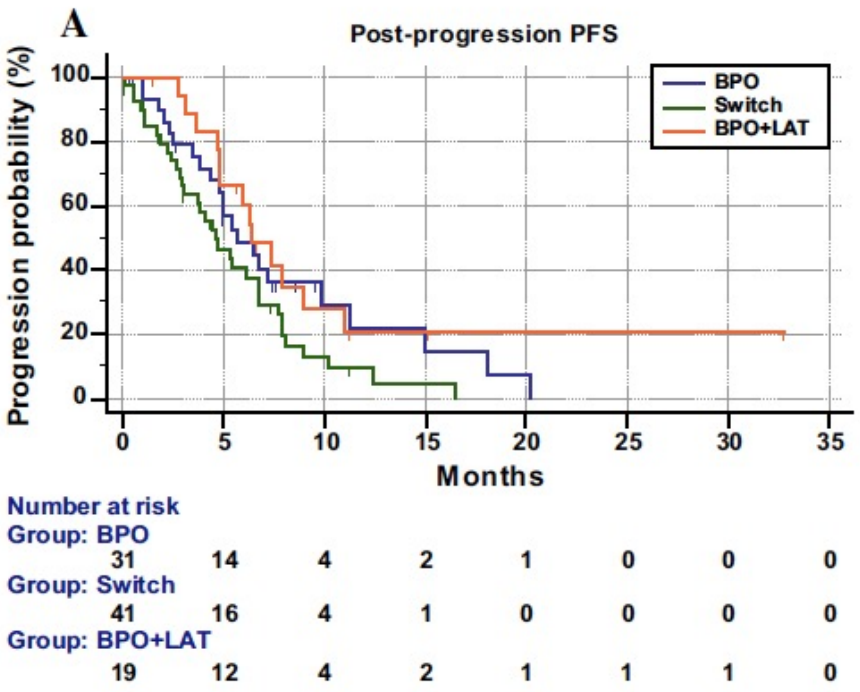
Schmid et al, Lung cancer 2019

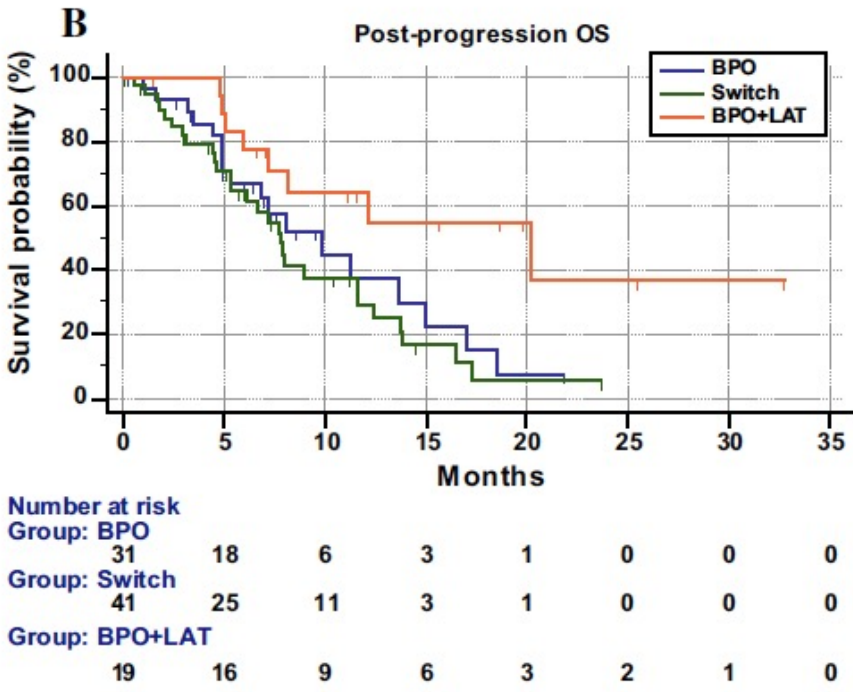
Oligoprogression and need for RT

Clinical and Translational Oncology
https://doi.org/10.1007/s12094-019-02193-w

RESEARCH ARTICLE

Osimertinib beyond disease progression in T790M *EGFR*-positive NSCLC patients: a multicenter study of clinicians' attitudes





Cortellini et al, Clinical and Translational Oncology 2019

FUTURE IN THE ERA OF TARGET THERAPY

Bone metastases in NSCLC and SREs

- ✓ Radiotherapy
- ✓ Bone surgery
- ✓ Pathological fractures
- ✓ Spinal cord compression
- ✓ Hypercalcemia

- ✓ Bone surgery
- ✓ Pathological fractures
- ✓ Spinal cord compression
- ✓ Hypercalcemia

RT = SREs ???

Not really !!!

TAKE HOME MESSAG

Headless Dancer ???