Trattamenti locali nel NSCLC metastatico
Trattamenti ablativi:
pratica corrente o ricerca clinica?

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BIOLOGICAL SCIENCES

1995: the term "oligometastases" is coined

Hellman S, Weichselbaum RR. J Clin Oncol. 1995;13(1):8-10

EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is

more about the multistep nature of the development of malignancy.[2,3] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[4] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized

- A counterpoint to the contiguous (Halsted) and systemic theories of cancer spread
- Cancer = spectrum from localized to widespread at time of diagnosis, with many intermediate states
  - Early metastases can be limited in number and location
  - "based on a state of limited metastatic capacity"

2011

OPINION

Oligometastases revisited

Weichselbaum, R. R. & Hellman, S. Nat. Rev. Clin. Oncol. 8, 378–382 (2011)

Is Definitive Therapy Justified in Lung Cancer Patients with Oligometastatic Disease ?

5-y Survival

Site	1976	1982	1994	2008
Breast	75	76	85	90
Colon	50	55	63	65
Prostate	67	73	93	100
Rectum	48	52	61	68
Lung	12	13	14	17

CA CANCER J CLIN 2013

Levels of Evidence in the Primary Literature

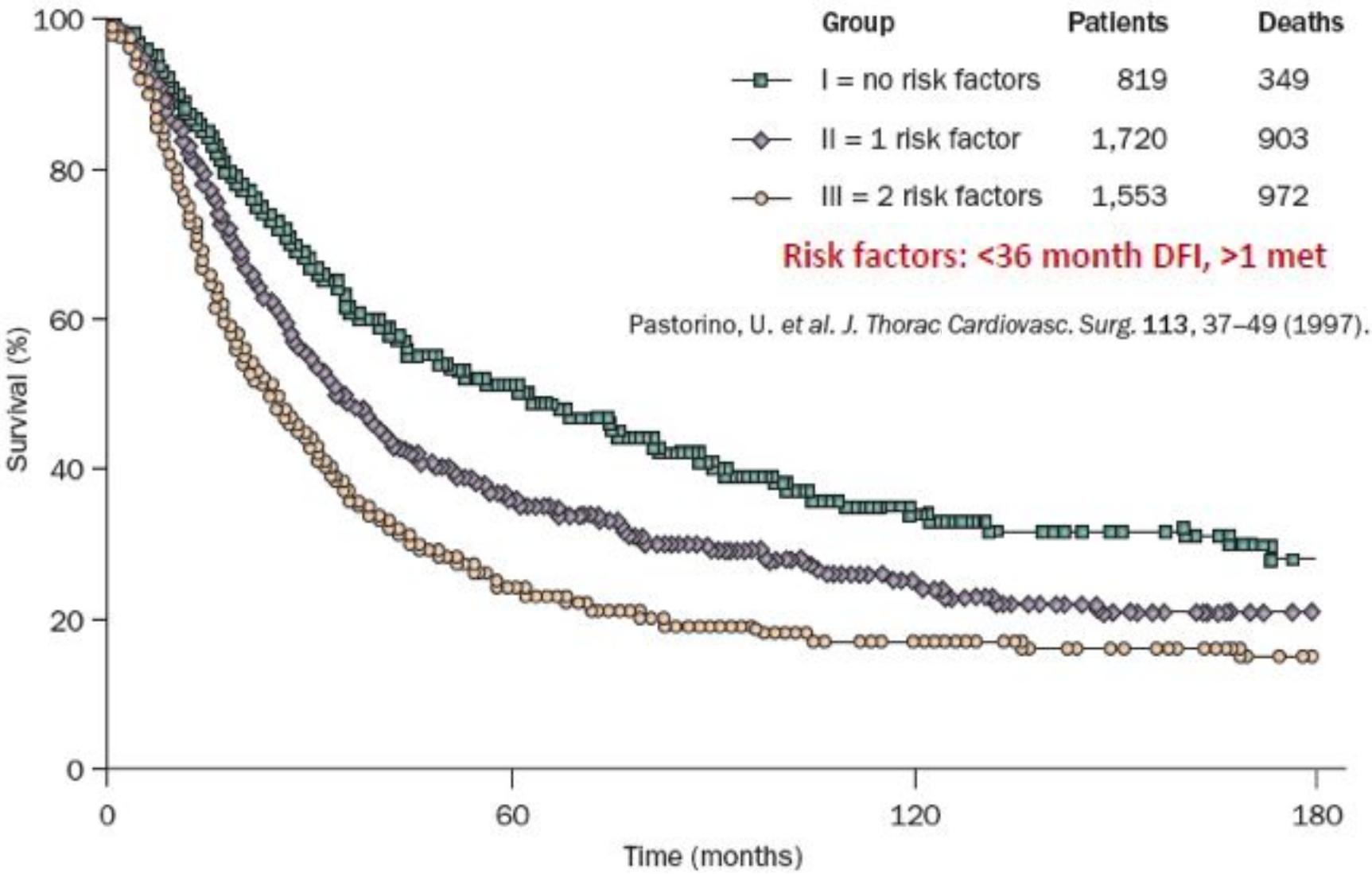
Stereotactic Ablative Radiotherapy for Pulmonary Oligometastases and Oligometastatic Lung Cancer

David Benjamin Shultz, MD, PhD, Andrea Riccardo Filippi, MD,† Juliette Thariat, MD,‡ Francoise Mornex, MD, PhD,‡ Billy W. Loo Jr, MD, PhD,* and Umberto Ricardi, MD†*

Ongoing Clinical Trials Examining the Role for Surgery or SABR for Oligometastatic Cancer

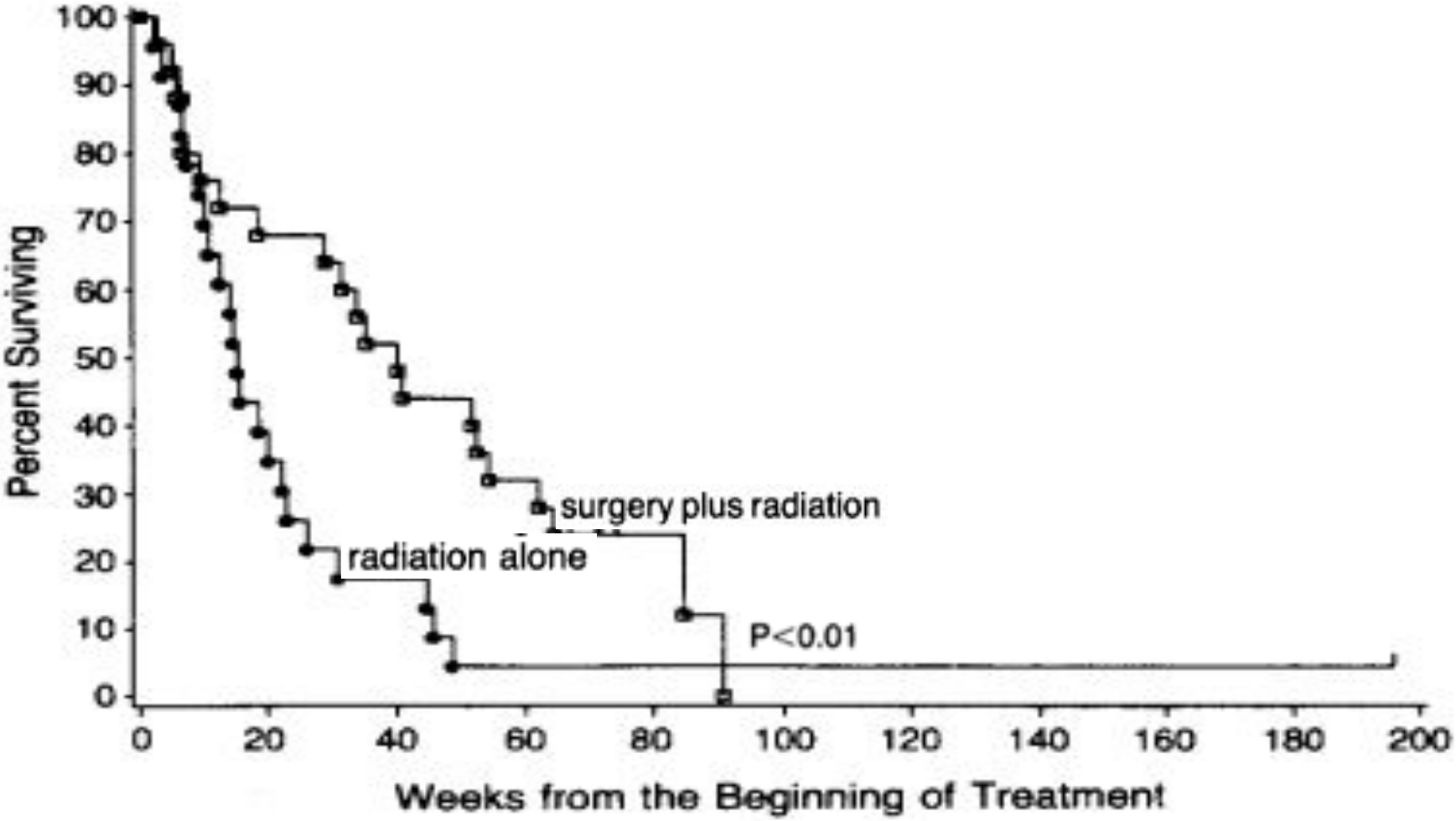
Study	Design	Eligibility	Intervention	Primary Endpoint
PulMICC[38]	Randomized phase II	Pulmonary metastases from colorectal cancer	Active monitoring vs. pulmonary metastasectomy	Feasibility/survival
SABR-COMET[39]	Randomized phase II	All treatable metastatic sites; maximum of three tumors to any single organ system; controlled primary tumor	Palliative-scheme radiation as clinically indicated vs. stereotactic ablative radiation to multiple sites	Overall survival
SAFRON II[40]	Randomized phase II	A maximum of three metastases to the lung from any nonhematological malignancy	Stereotactic multifraction SABR vs. radiosurgery	Toxicity
NCT01185639[41]	Phase II	NSCLC with ≤5 metastatic sites, involving lung, liver, adrenal, or spinal lesions; if primary untreated, must have three mets	SBRT to affected sites, delivered in three or five fractions	Progression-free survival
NCT01725165[72]	Randomized phase II	Three or less metastases from NSCLC	Consolidative radiotherapy and/or surgery vs. systemic therapy or observation	Progression-free survival

Surgery for Lung Metastases



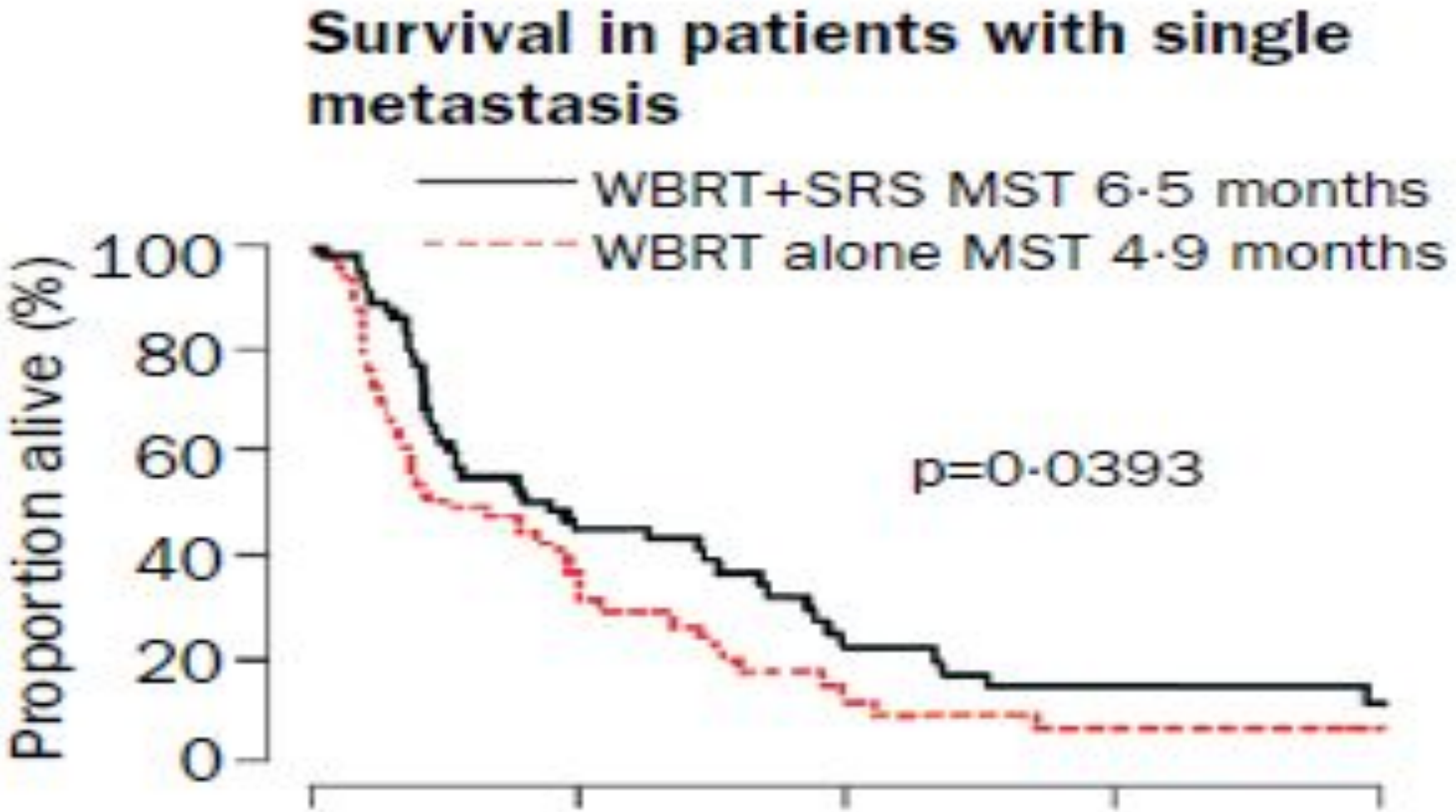
A RANDOMIZED TRIAL OF SURGERY IN THE TREATMENT OF SINGLE METASTASES TO THE BRAIN

ROY A. PATCHELL, M.D., PHILLIP A. TIBBS, M.D., JOHN W. WALSH, M.D., ROBERT J. DEMPSEY, M.D., YOSH MARUYAMA, M.D., RICHARD J. KRYSCIO, PH.D., WILLIAM R. MARKESBERY, M.D., JOHN S. MACDONALD, M.D., AND BYRON YOUNG, M.D.



Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial

THE LANCET • Vol 363 • May 22, 2004



Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): Patient outcomes and prognostic factors

Gwendolyn H.M.J. Griffioen[a,*], Daniel Toguri[b], Max Dahele[a], Andrew Warner[b], Patricia F. de Haan[a], George B. Rodrigues[b], Ben J. Slotman[a], Brian P. Yaremko[b], Suresh Senan[a], David A. Palma[b]

- From 1999-2012, 61 NSCLC patients with 1-3 oligomets received definitive treatment to all sites of disease, pooled from 2 large cancer centers in Netherlands and Canada

- 82% solitary met, 15% 2 mets, 3% 3 mets

- Location: 59% brain; 18% bone; 7% each for contralateral lung, adrenal, and distant LN.

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Treatment primary lung tumor – *n*(%)	
Concurrent CRT	30 (49.2)
Sequential CRT	10 (16.4)
Primary RT	2 (3.3)
Stereotactic RT	10 (16.4)
Trimodality (surgery + CRT)	3 (4.9)
Surgery + CT	3 (4.9)
Surgery only	3 (4.9)

Treatment to metastases – *n*(%)	
Stereotactic RT	24 (39.3)
Intracranial	18 (29.5)
Extracranial	6 (9.8)
Conventional RT (EBRT)	13 (21.3)
Surgery	6 (9.8)
WBRT + Boost	2 (3.3)
Surgery + RT	16 (26.2)

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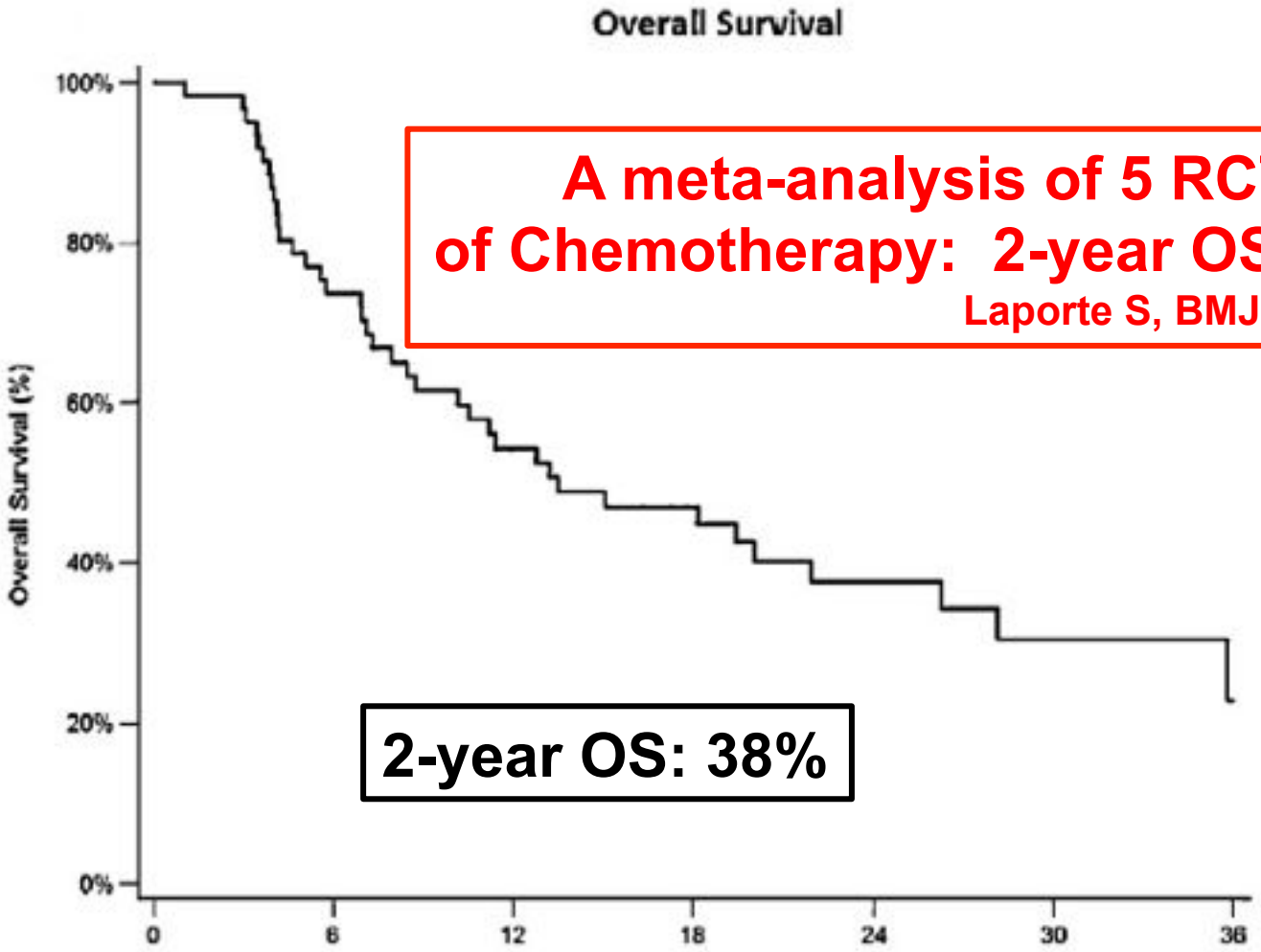


A meta-analysis of 5 RCTs of Chemotherapy: 2-year OS = 20%

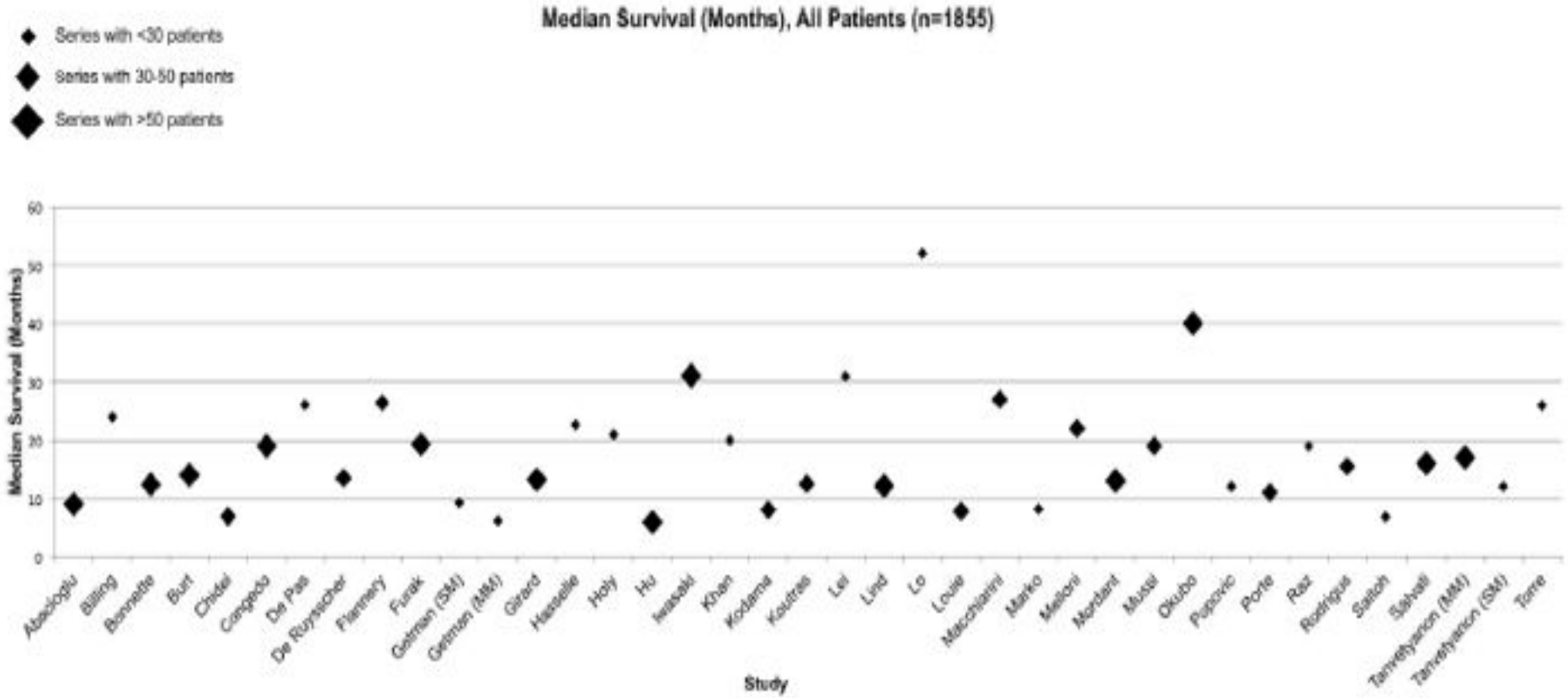
Laporte S, BMJ Open 2013

2-year OS: 38%

Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature

Allison Ashworth, George Rodrigues, Gabriel Boldt, David Palma*

5 year OS: 23.3% (8.3–86%)



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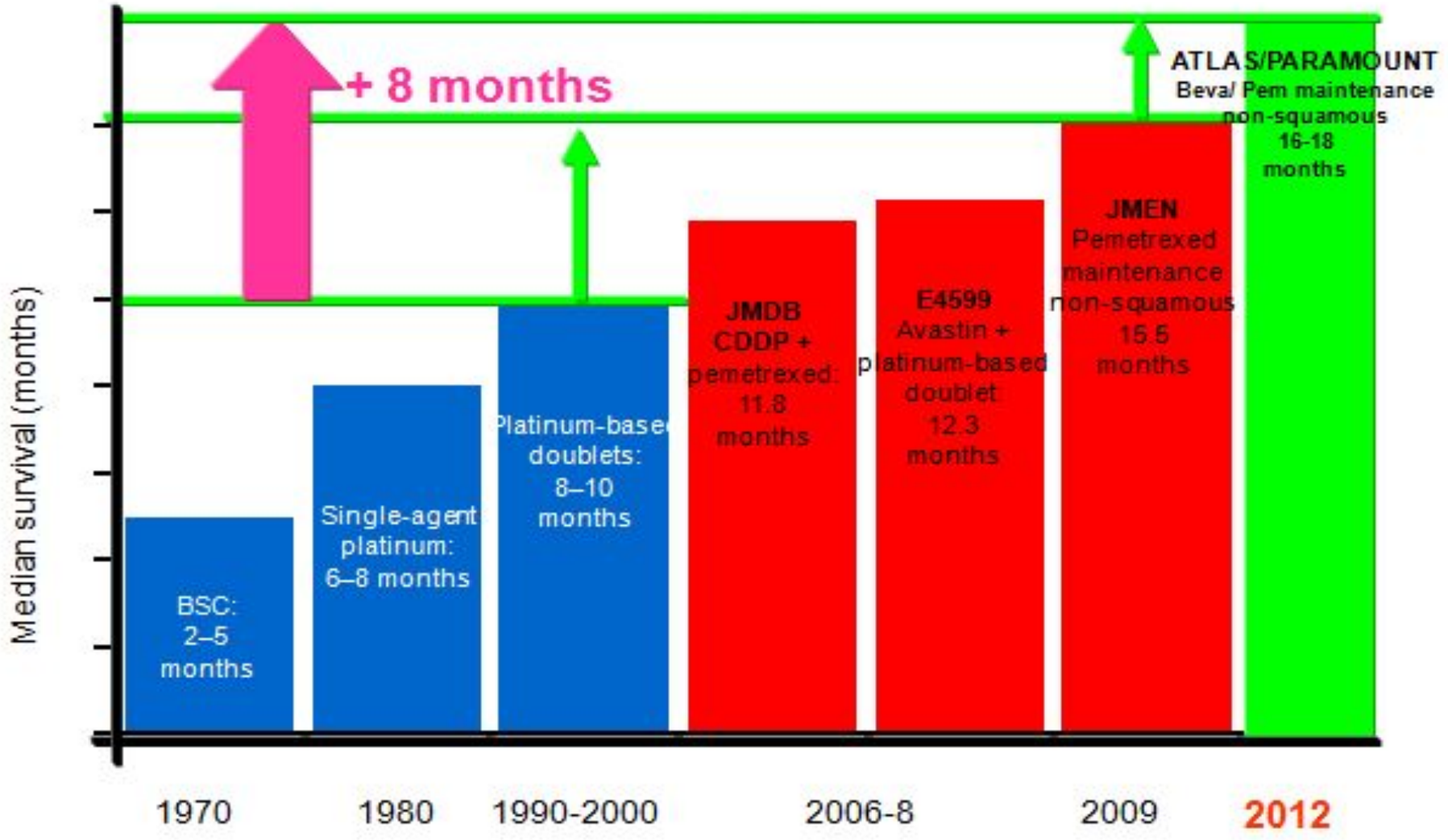


Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature

Allison Ashworth, George Rodrigues, Gabriel Boldt, David Palma*

- **60% of studies included patients with brain metastases only**
- **neither intervention is supported by level 1 evidence from RCTs**

long-term survival reflective of patient selection, or a treatment effect ?

Radical Treatment of Non–Small-Cell Lung Cancer Patients with Synchronous Oligometastases

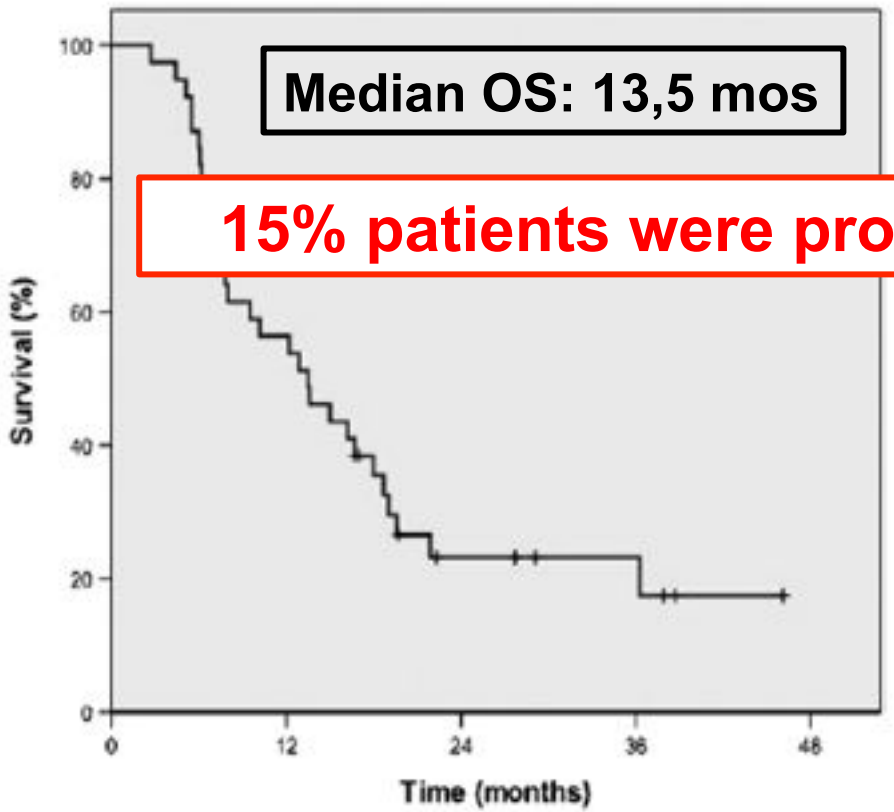
Long-Term Results of a Prospective Phase II Trial (Nct01282450)

Dirk De Ruysscher, MD, PhD,# Rinus Wanders, MD,* Angela van Baardwijk, MD, PhD,* Anne-Marie C. Dingemans, MD, PhD,† Bart Reymen, MD,* Ruud Houben, MSc,* Gerben Bootsma, MD, PhD,‡ Cordula Pitz, MD, PhD,§ Linda van Eijsden, MD,¶ Wiel Geraedts, MD,|| Brigitta G. Baumert, MD, PhD,* and Philippe Lambin, MD, PhD**

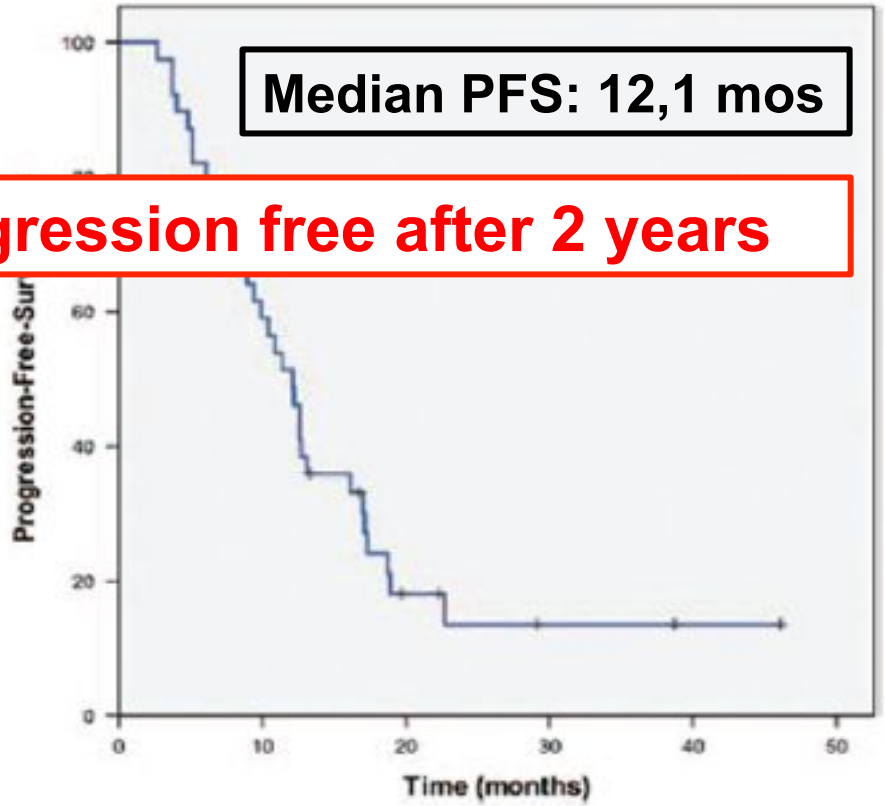
Median OS: 13,5 mos

Median PFS: 12,1 mos

15% patients were progression free after 2 years



Overall survival ($n = 39$).



Progression-free survival.

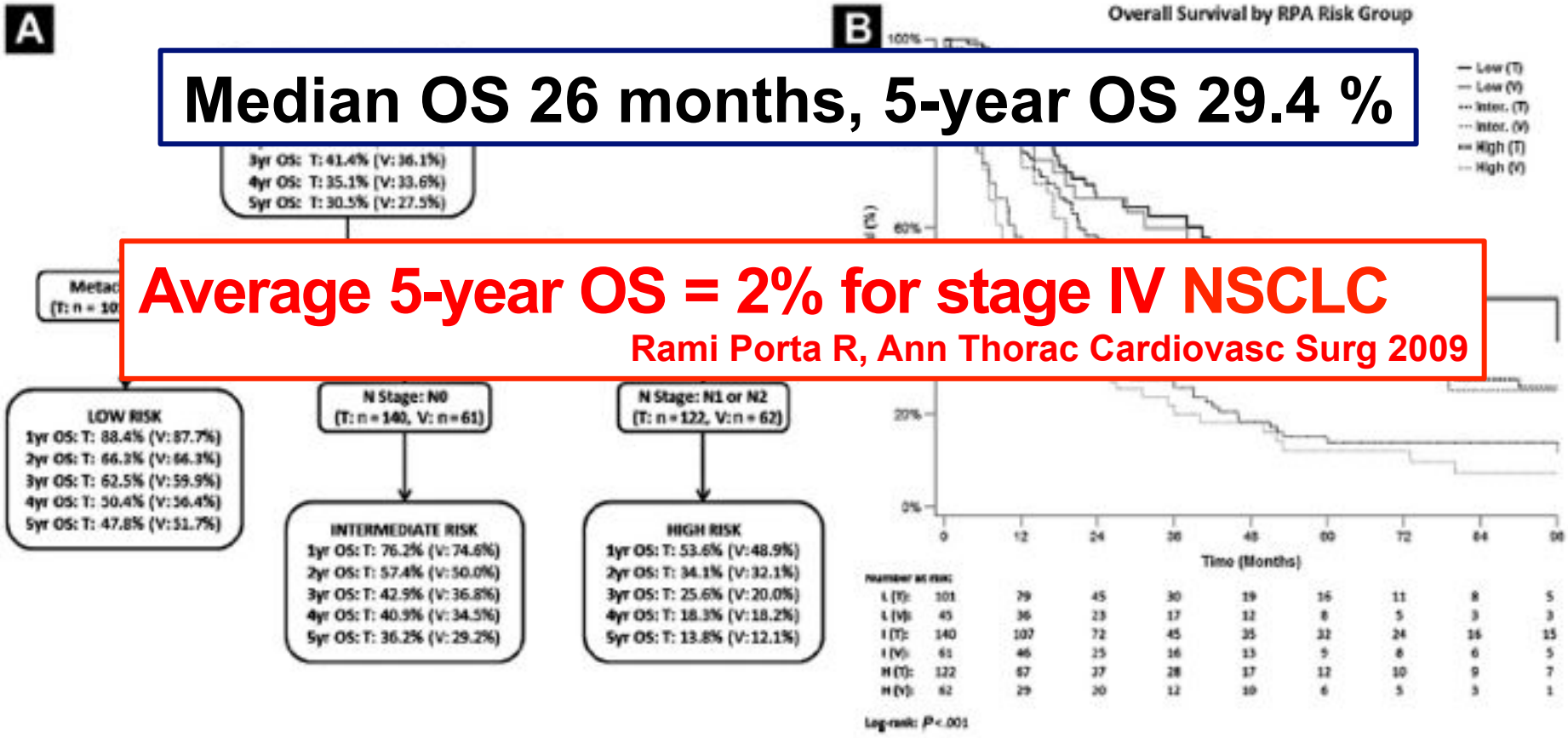
An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non–Small-Cell Lung Cancer

Allison B. Ashworth,[1] Suresh Senan,[2] David A. Palma,[1] Marc Riquet,[3] Yong Chan Ahn,[4] Umberto Ricardi,[5] Maria T. Congedo,[6] Daniel R. Gomez,[7] Gavin M. Wright,[8] Giulio Melloni,[9] Michael T. Milano,[10] Claudio V. Sole,[11] Tommaso M. De Pas,[12] Dennis L. Carter,[13] Andrew J. Warner,[1] George B. Rodrigues[1]

Median OS 26 months, 5-year OS 29.4 %

Average 5-year OS = 2% for stage IV NSCLC

Rami Porta R, Ann Thorac Cardiovasc Surg 2009



A Call for the Aggressive Treatment of Oligometastatic and Oligo-Recurrent Non-Small Cell Lung Cancer

Pretesh R. Patel,[1] David S. Yoo,[1] Yuzuru Niibe,[2] James J. Urbanic,[3] and Joseph K. Salama[1]

Analysis of further disease progression in metastatic non-small cell lung cancer: Implications for locoregional treatment

Table IV. Outcome of all 38 patients.

No progression of disease	12 patients
Progression only at sites of initial involvement	7 patients
Development of new metastases in an organ that was initially involved with tumor	3 patients
Development of new metastasis in an organ that was not initially uninvolved with tumor	14 patients (6 also developed more metastases in an organ that was previously involved with tumor)
No follow-up scans	2 patients

50%

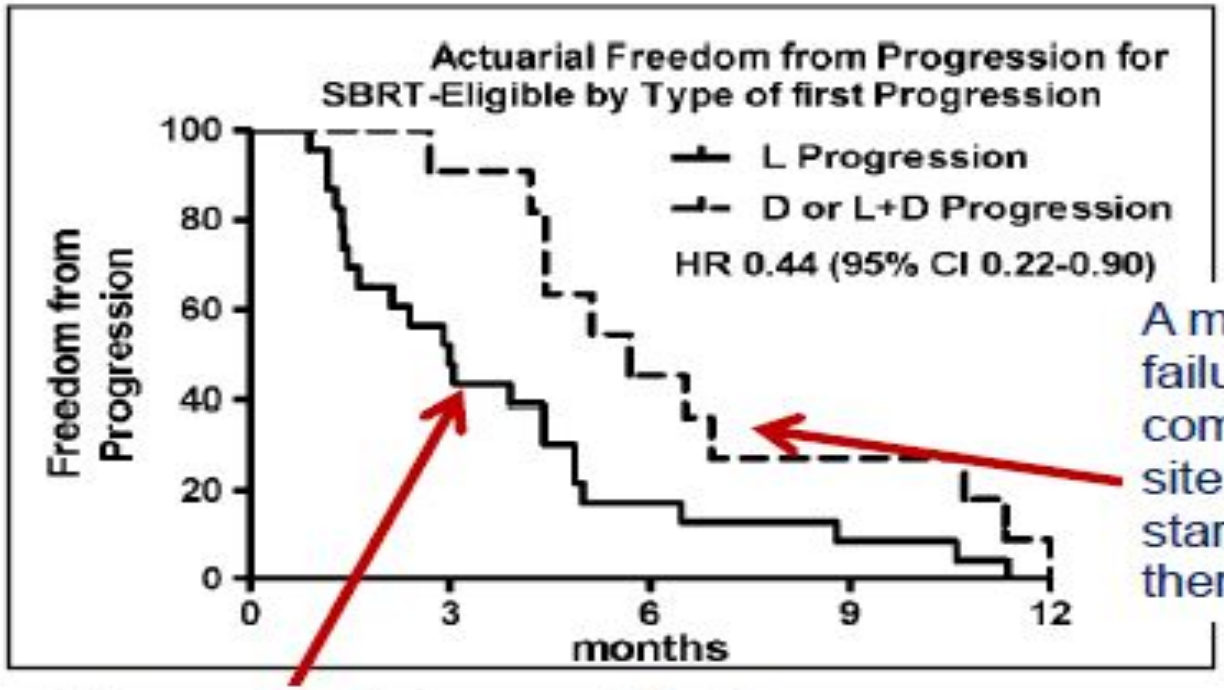
Table V. Outcome of 17 patients who had ≤4 sites of involvement in addition to the primary tumor

No progression of disease	7 patients
Progression only at sites of initial involvement	4 patients
Development of new metastases in an organ that was initially involved with tumor	1 patient
Development of new metastasis in an organ that was not initially uninvolved with tumor	5 patients

65%

Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis

Patterns of Failure in metastatic NSCLC



Rusthoven et al, Acta Oncol 2009

A minority have first failure with a component in a distant site not present at the start of systemic therapy

After 1st line systemic therapy, 2/3 of patients have first failure in initially involved sites, with median PFS of 3 mos

EXPERT REVIEWS

Moving from histological subtyping to molecular characterization: new treatment opportunities in advanced non-small-cell lung cancer

Expert Rev. Anticancer Ther. Early online, 1–19 (2014)

Simona Carnio,
Silvia Novello,
Paolo Bironzo and
Giorgio Vittorio
Scagliotti*

Department of Oncology, S. Luigi Hospital, University of Torino, Regione Gonzole 10, 10043 Orbassano, Torino, Italy
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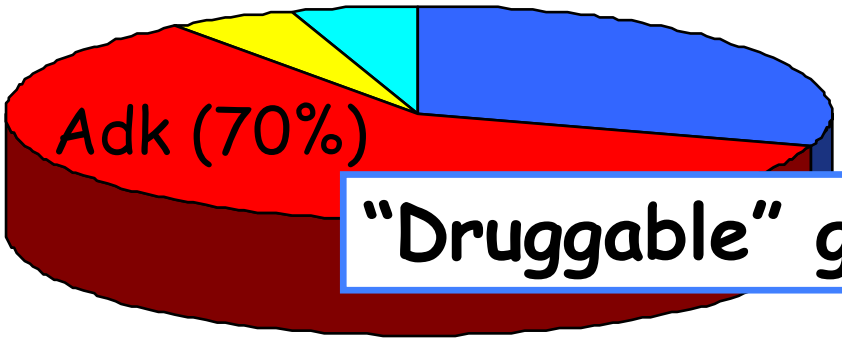
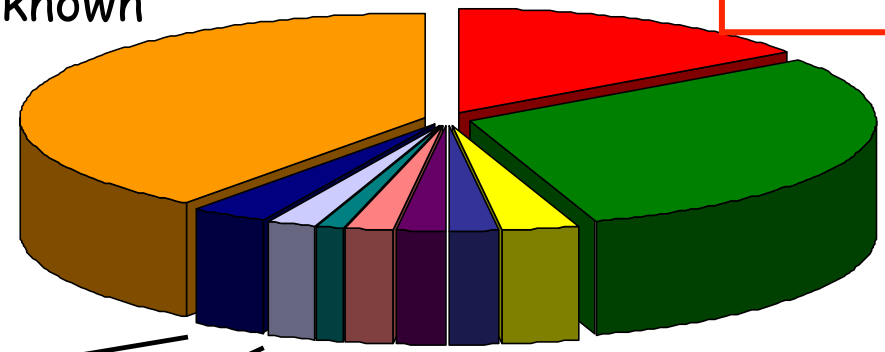
Non Small Cell Lung Cancer: From Histology To Genomics



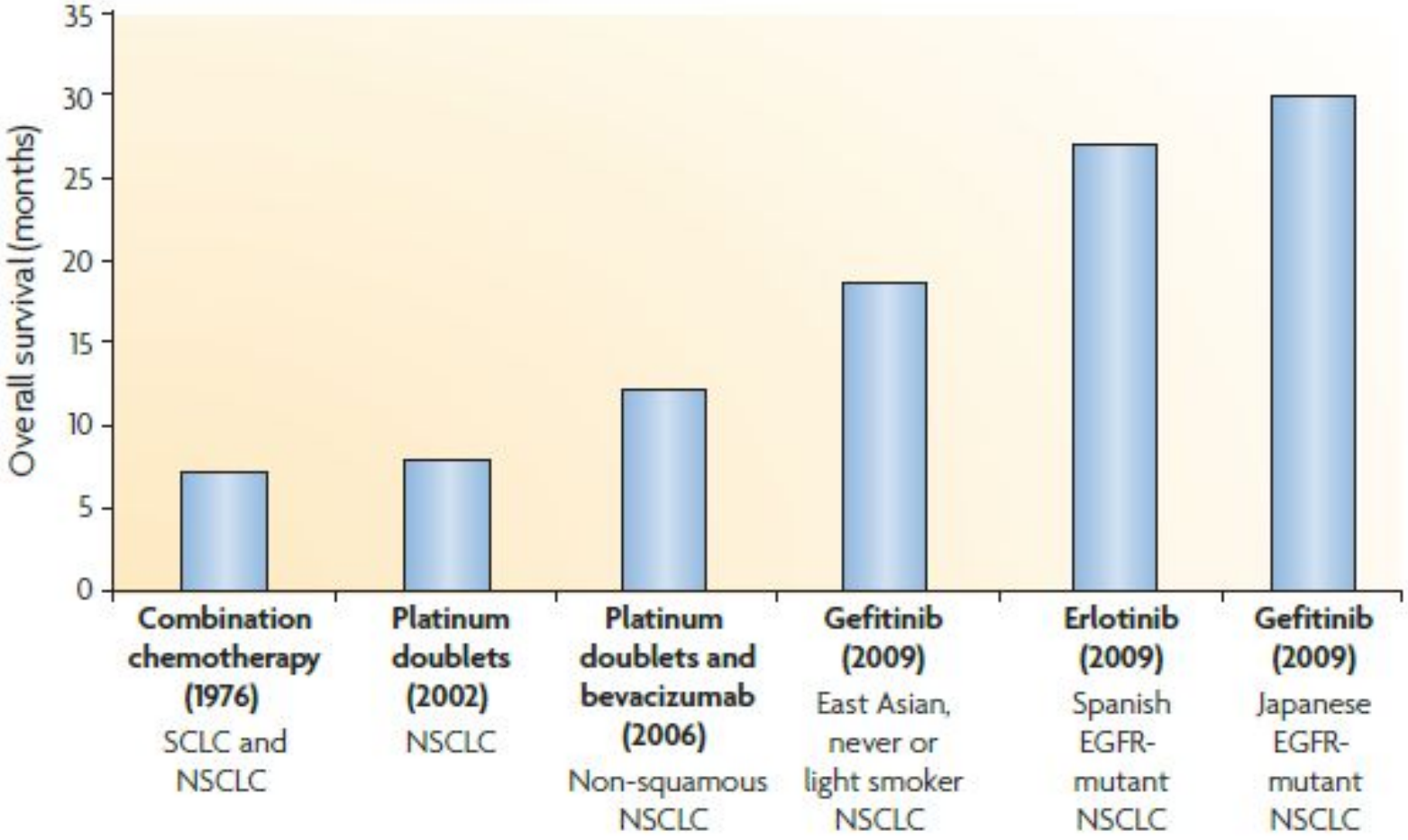
"Druggable" genomic alterations

Kinases

Critical to growth & survival of NSCLC



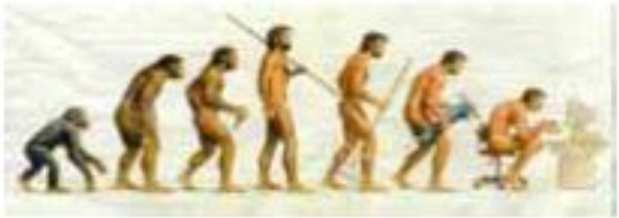
The targeted therapy revolution: patients with advanced, unresectable lung cancer now live longer



Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nat Rev Cancer. 2010; 10: 760–774.

The “Darwinian” oncology

Why the ~~house~~ cancer will always win at this point:



The odds are 40,000,000,000+ to 1 in favor of the cancer

ie,

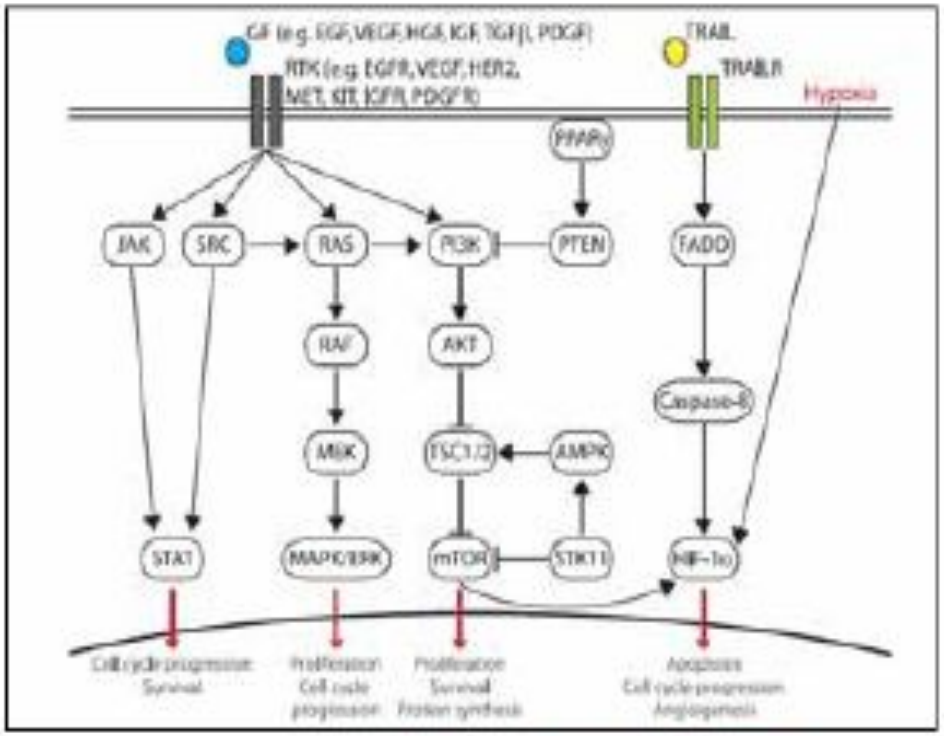
$4x10^{10+}$ cancer cells

vs.

1 drug blocking 1 pathway

Some cells will not be driven by the pathway being blocked. These cells will “evolve” by Darwinian selection and grow.

Targeted therapies: molecular vs spatial



Larsen J, et al. Cancer J 2011;17: 512-527

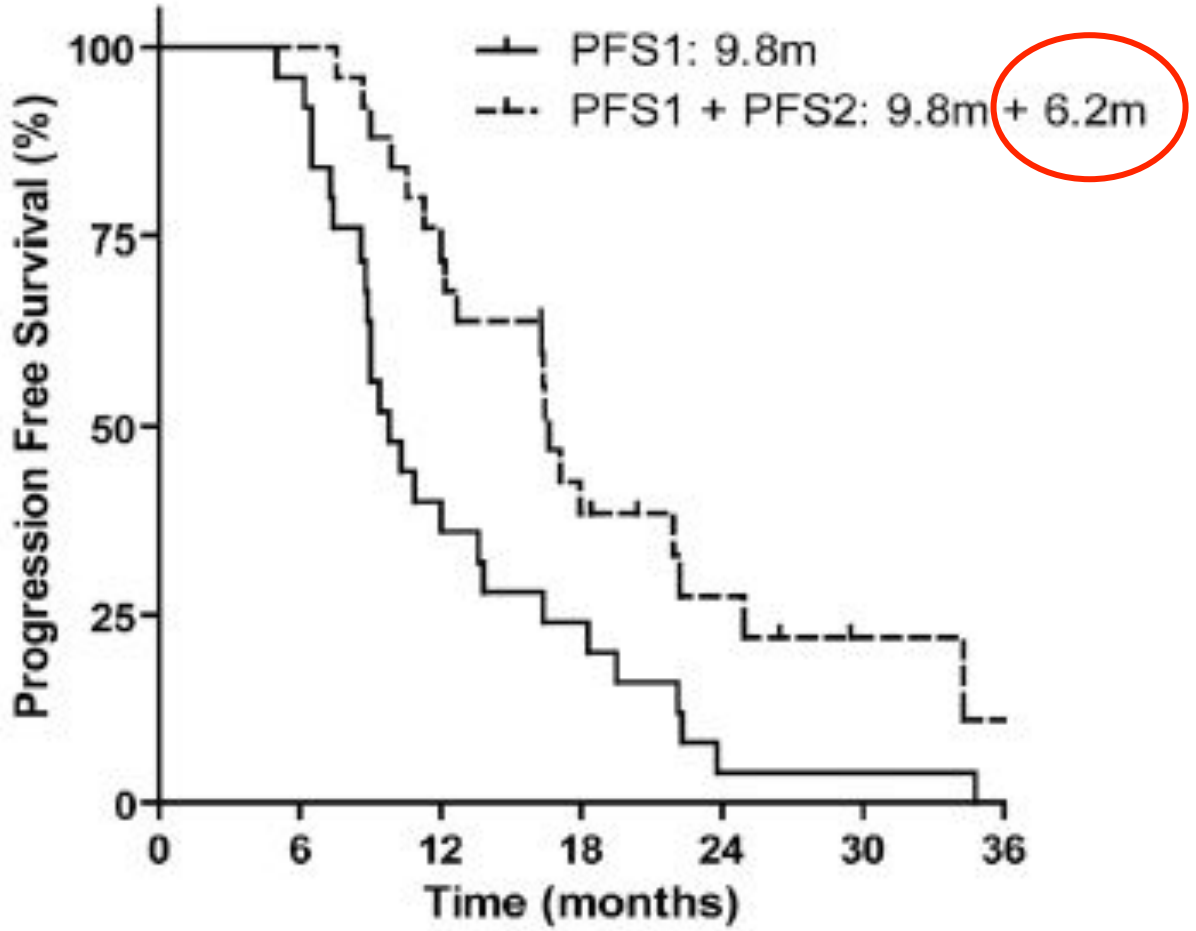
Radiation therapy:
Spatially targeted

Great if you find an Achilles heel pathway
Eventually, some resistant cells emerge

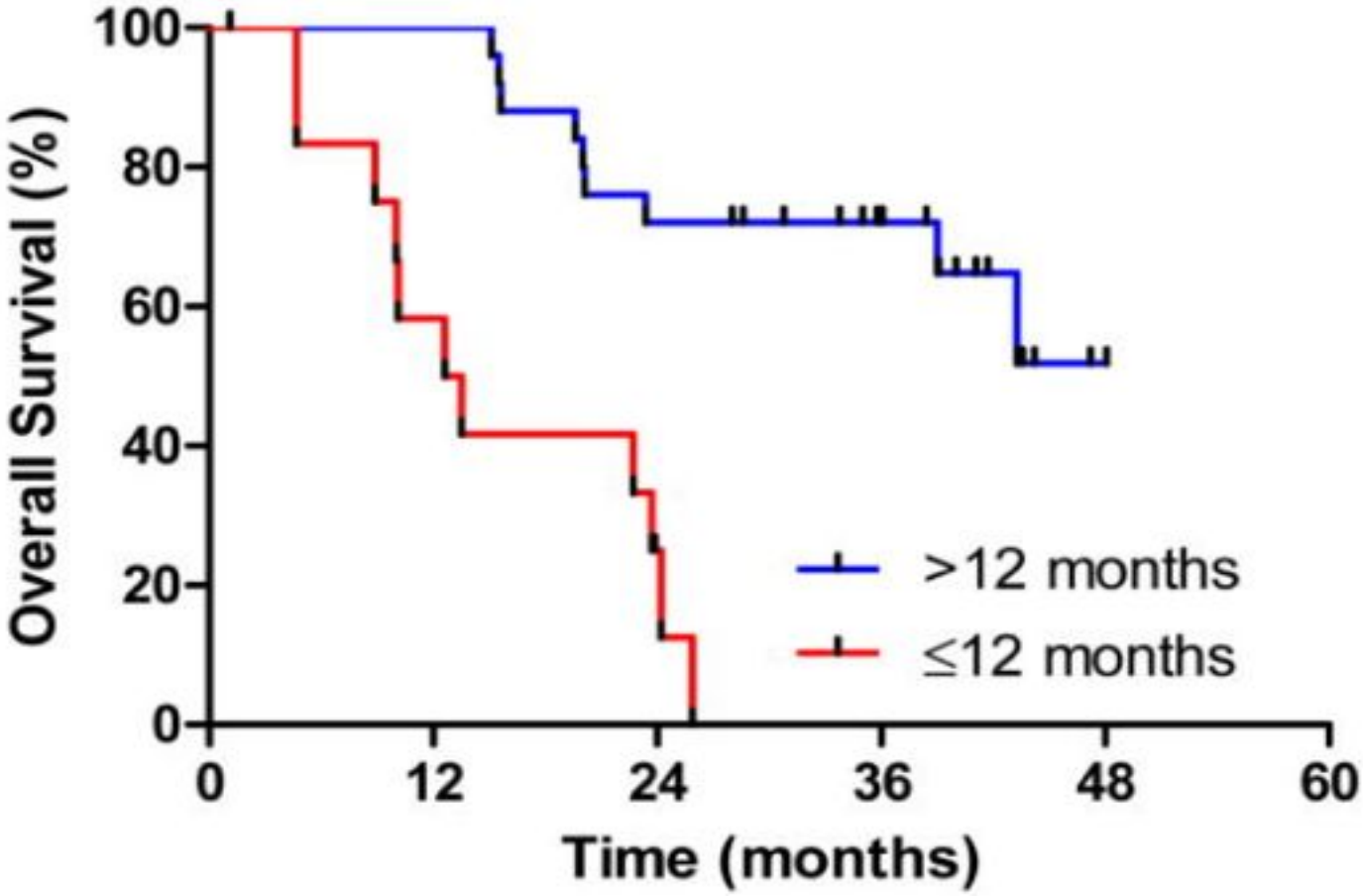
All cells susceptible, given enough dose
Nearby normal tissues limit tolerance

Local Ablative Therapy of Oligoprogressive Disease Prolongs Disease Control by Tyrosine Kinase Inhibitors in Oncogene-Addicted Non–Small-Cell Lung Cancer

PFS of all patients treated with LAT and continuation of TKI therapy



Stereotactic Radiotherapy Can Safely and Durably Control Sites of Extra-CNS Oligoprogressive Disease in ALK-Positive Lung Cancer Patients on Crizotinib



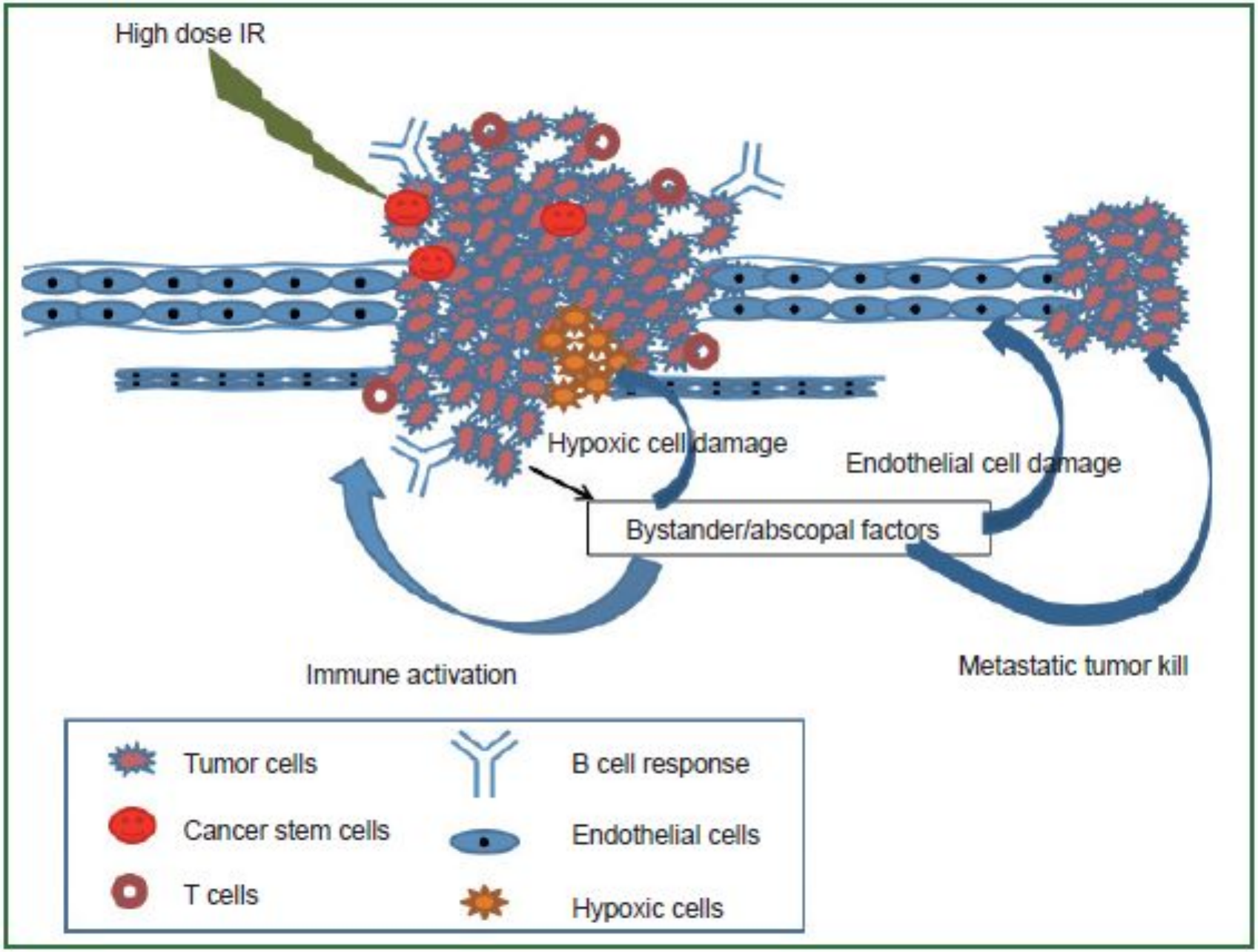
Longer time on the active agent was associated with improved OS

Editorial

Practical Radiation Oncology (2011) 1, 38–39

Stereotactic ablative radiotherapy: what's in a name?

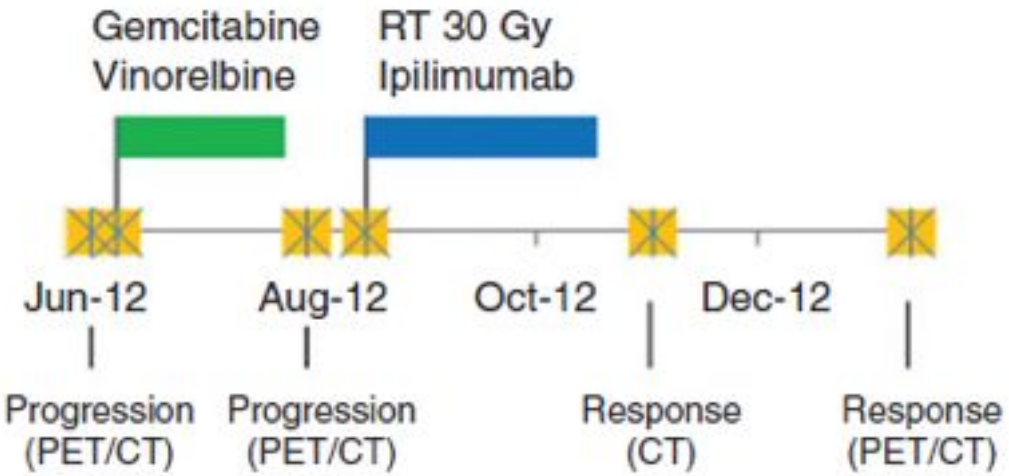
Billy W. Loo Jr MD, PhD[a,*], Joe Y. Chang MD, PhD[b], Laura A. Dawson MD, FRCPC[c], Brian D. Kavanagh MD, MPH[d], Albert C. Koong MD, PhD[a], Suresh Senan MRCP, FRCR, PhD[e], Robert D. Timmerman MD[f]

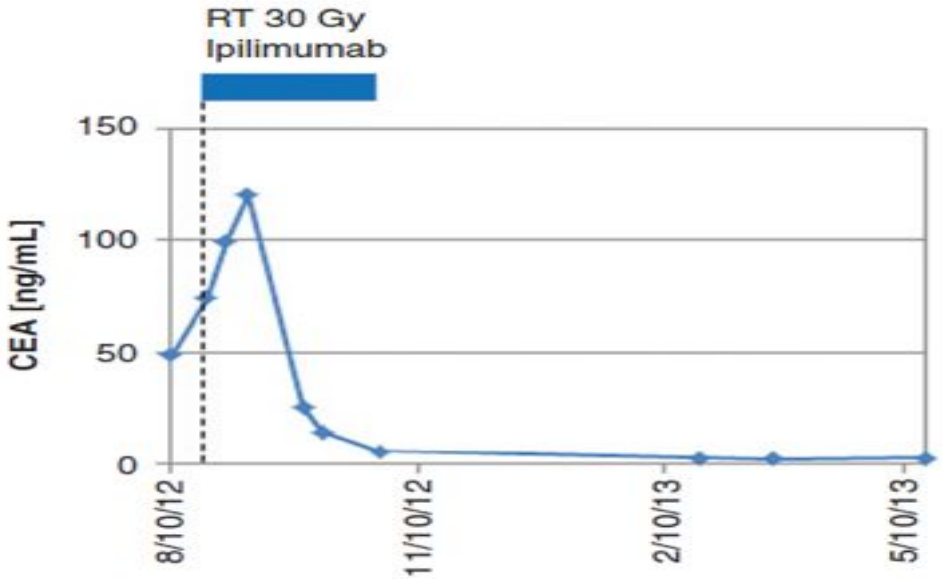

High dose IR
Hypoxic cell damage
Endothelial cell damage
Bystander/abscopal factors
Immune activation
Metastatic tumor kill
Tumor cells
Cancer stem cells
T cells
B cell response
Endothelial cells
Hypoxic cells

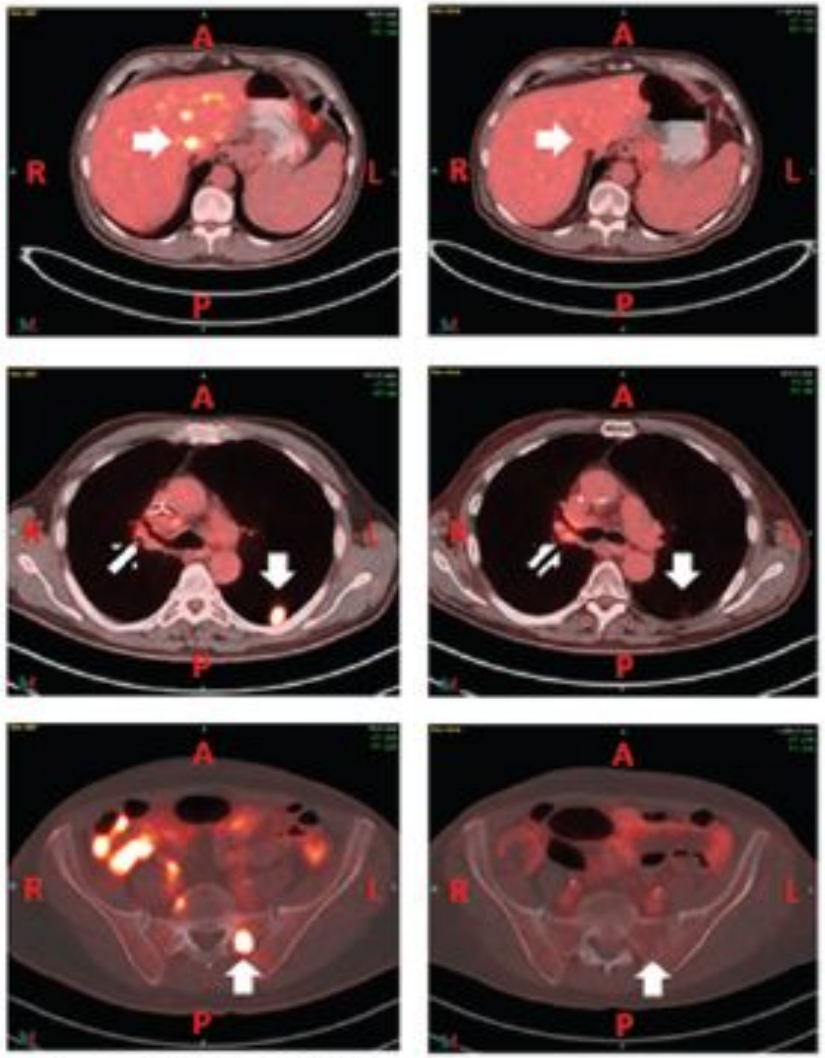
An Abscopal Response to Radiation and Ipilimumab in a Patient with Metastatic Non–Small Cell Lung Cancer

Cancer Immunology Research

Encouse B. Golden[1], Sandra Demaria[1,2], Peter B. Schiff[1], Abraham Chachoua[3], and Silvia C. Formenti[1]







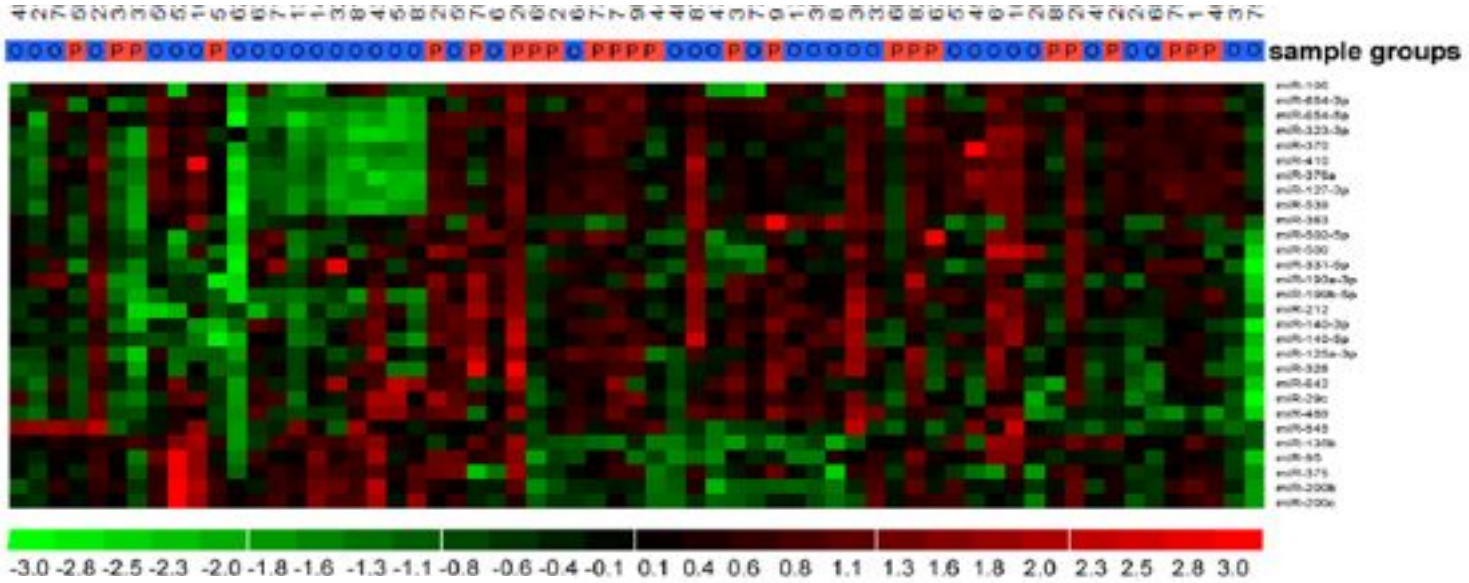
August 2012 PET/CT

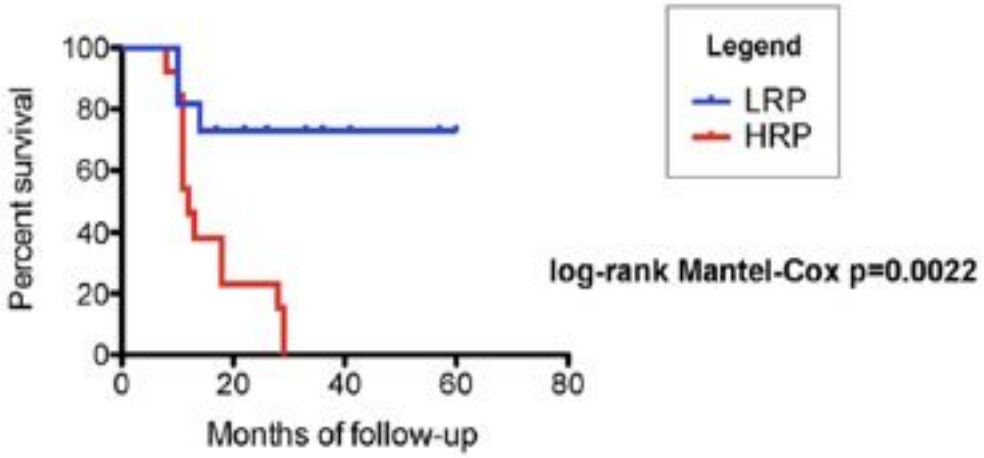
January 2013 PET/CT

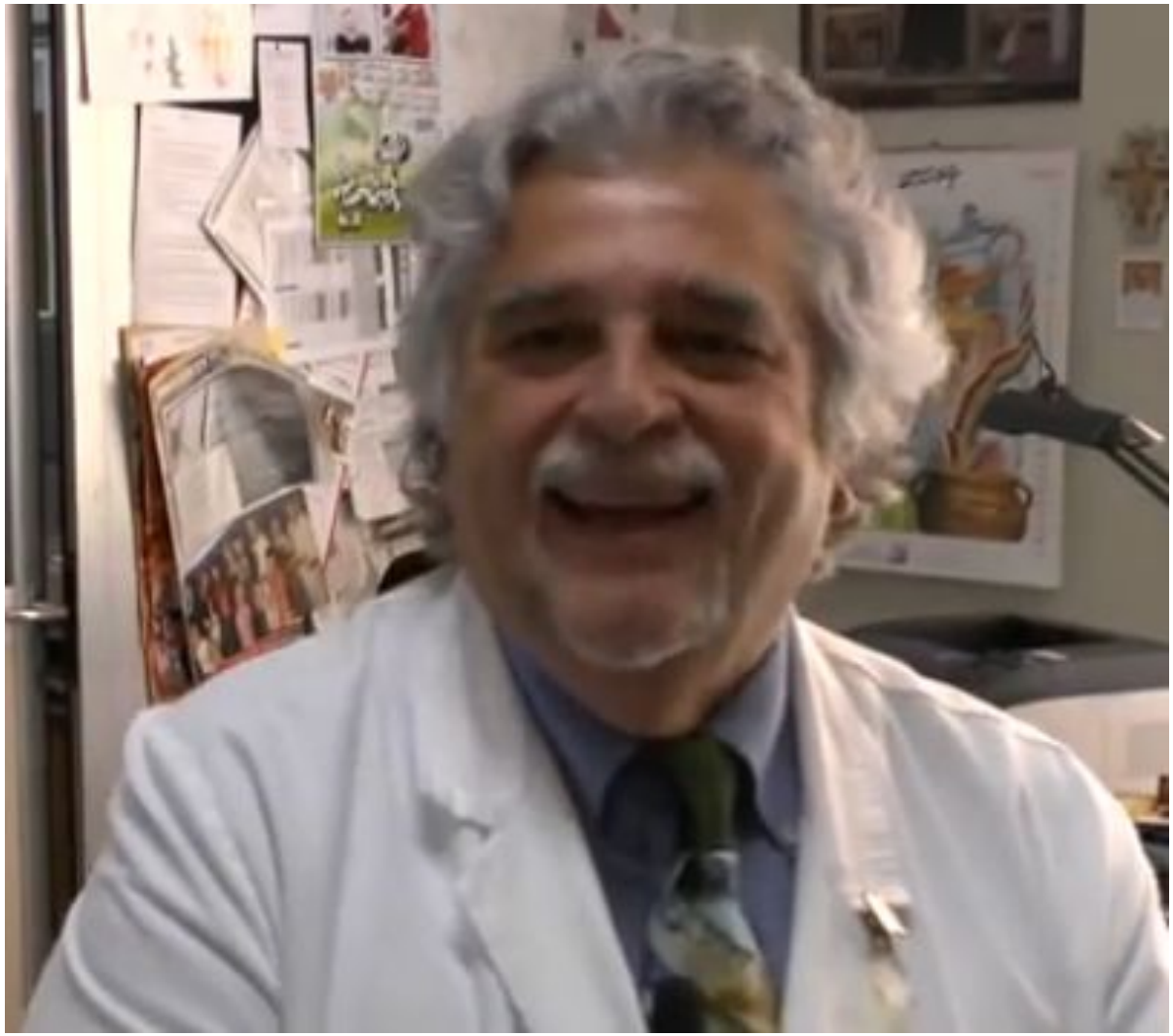
OPEN ACCESS Freely available online

PLOS | ONE

Oligo- and Polymetastatic Progression in Lung Metastasis(es) Patients Is Associated with Specific MicroRNAs







Ciao, Mauro