DICHIARAZIONE

Relatore: Francesco Pasqualetti

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board:**NIENTE DA DICHIARARE**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Altro

Società Italiana di Radiobiologia

XXVI CONGRESSO NAZIONALE AIRO
XXX CONGRESSO NAZIONALE AIRB
IX CONGRESSO NAZIONALE AIRO GIOVANI

"Effetti biologici dei farmaci a bersaglio molecolare sulle metastasi cerebrali"

Dr. Francesco Pasqualetti

U.O. Radioterapia Universitaria
Azienda Ospedaliero Universitaria Pisana

A **Valid Target** is: A target that when modulated pharmacologically, provides meaningful efficacy and acceptable safety for specific human disease in longterm clinical usage.

Target Validation is: The process of demonstrating in a clinical trial that engaging the target provides statistically meaningful therapeutic benefit with acceptable safety for a given indication.

Target Qualification is: Preclinical or limited clinical studies prior to well powered clinical trials, that establish the scientific validity and safety of a drug target; it is part of the continuum of target validation.

Target Identification is: The generation of scientific evidence that a manipulatable able target is involved in some significant way in a disease process

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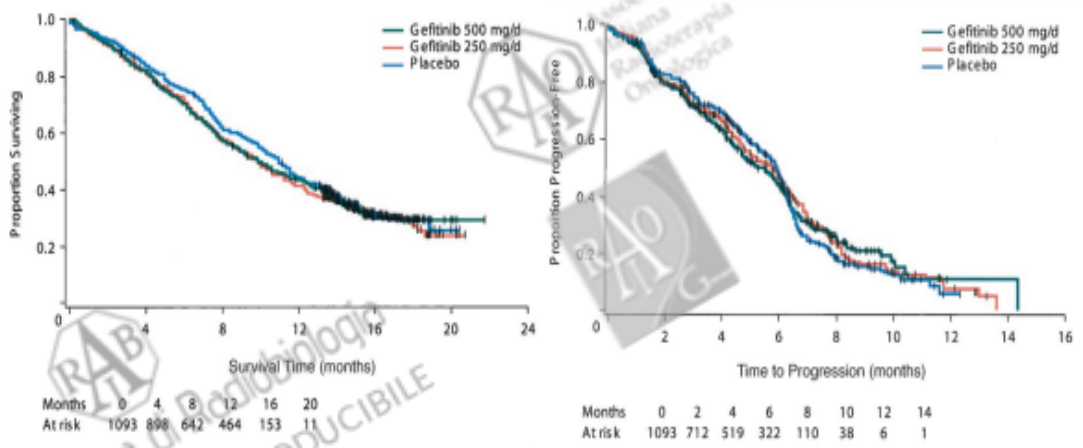
VOLUME 22 · NUMBER 5 · MARCH 1 2004
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Gefitinib in Combination With Gemcitabine and Cisplatin in Advanced Non–Small-Cell Lung Cancer: A Phase III Trial—INTACT 1

Giuseppe Giaccone, Roy S. Herbst, Christian Manegold, Giorgio Scagliotti, Rafael Rosell, Vincent Miller, Ronald B. Natale, Joan H. Schiller, Joachim von Pawel, Anna Pluzanska, Ulrich Gatzemeier, John Grous, Judith S. Ochs, Steven D. Averbuch, Michael K. Wolf, Pamela Rennie, Abderrahim Fandi, and David H. Johnson



The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

N Engl J Med 2004; 350:2129-2139 | May 20, 2004 | DOI: 10.1056/NEJMoa040938

CONCLUSIONS

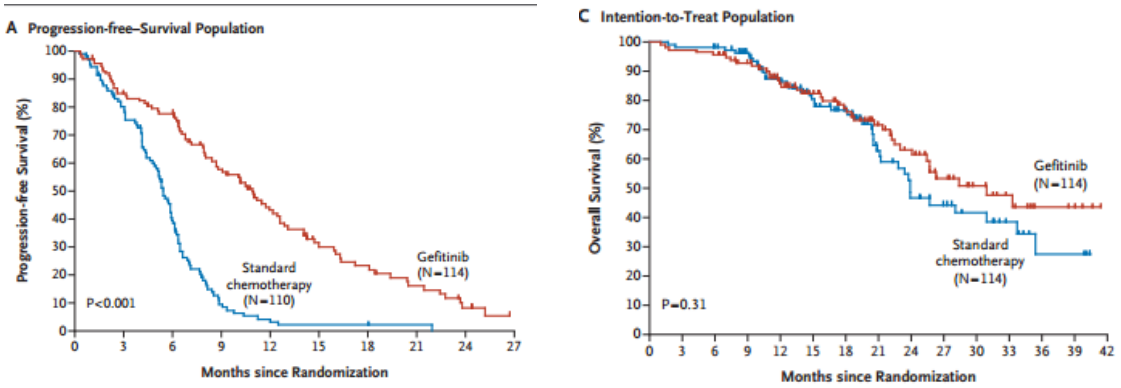
A subgroup of patients with non–small-cell lung cancer have specific mutations in the *EGFR* gene, which correlate with clinical responsiveness to the tyrosine kinase inhibitor gefitinib. These mutations lead to increased growth factor signaling and confer susceptibility to the inhibitor. Screening for such mutations in lung cancers may identify patients who will have a response to gefitinib.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

Makoto Maemondo, M.D., Ph.D., Akira Inoue, M.D., Ph.D., Kunihiko Kobayashi, M.D., Ph.D., Shunichi Sugawara, M.D., Ph.D., Satoshi Oizumi, M.D., Ph.D., Hiroshi Isobe, M.D., Ph.D., Akihiko Gemma, M.D., Ph.D., Masao Harada, M.D., Ph.D., Hirohisa Yoshizawa, M.D., Ph.D., Ichiro Kinoshita, M.D., Ph.D.,



200,000 cases of brain metastases occur each year in the US

20-40% of patients with systemic cancers develops brain metastasis during the course of their disease (withan an ever greater incidence at autopsy)

Brain metastases are associated with poor prognosis, neurological deterioration, diminished quality of life, short survival

Most brain metastasis are the prodict of primary tumor that originate in the lung (40%-50%), breast (15%-20%), skin (5%-10%)

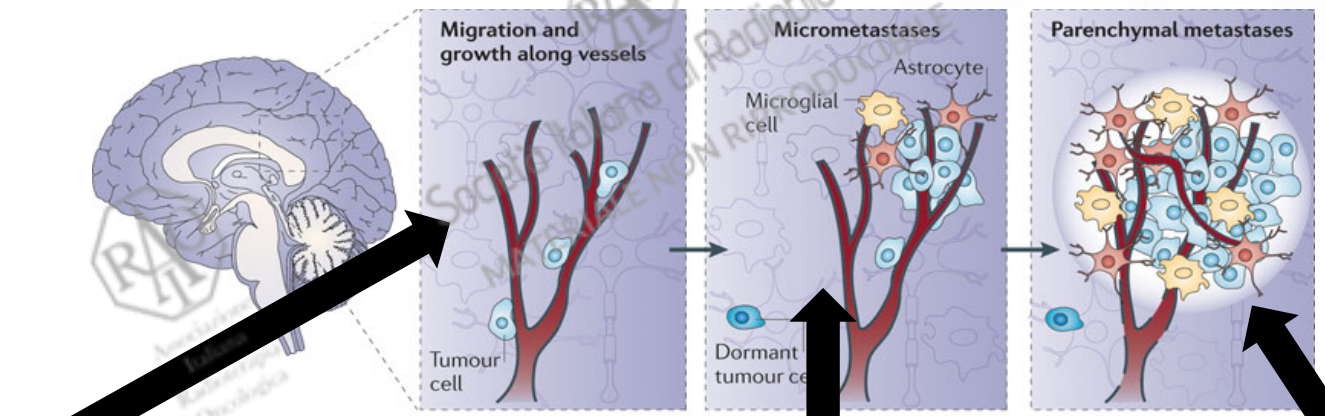
Gavrilovic IT, J Neurooncol 2005
Patchell RA, Cancer Treat Rev 203
Cruz-Munoz W, Semin cancer Biol 2001
Lassman AB, Neurol Clin 2003

Metastases are the end result of a multistage process

- **Local invasion by the primary tumor**
- **Intravasation into the blood or lymphatic system**
- **Survival in circulation**
- **Arrestat distant organ and metastatic colonization**

Obenauf, A.C., Trends in Cancer, 2015

Brain metastases are the end result of further multistage process



Patricia S. Steeg, Nature Reviews | Cancer

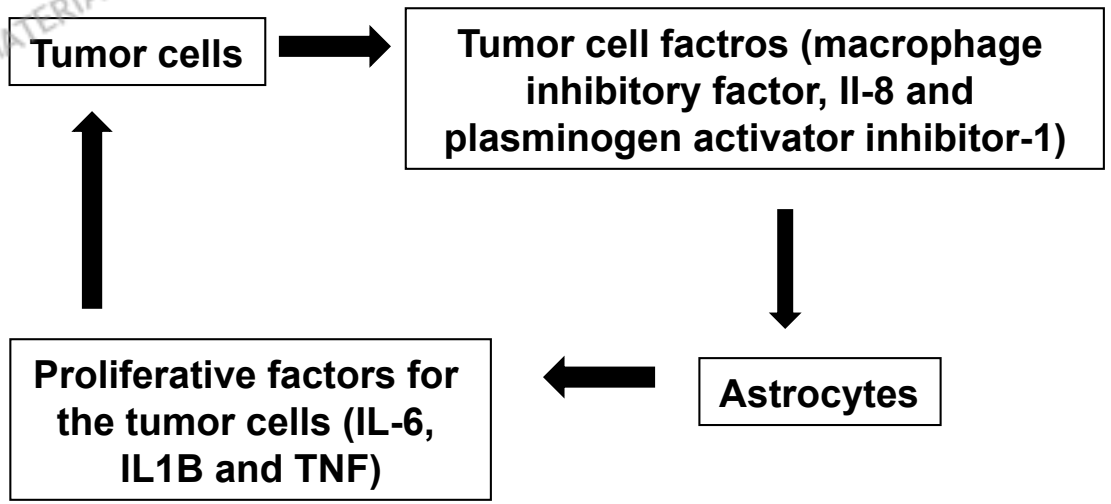
Tumor cells elongate their shape along vessel, adhere to the vascular basement membrane via B1 integrins.

Tumor cells proliferate and invade while on top of the vascular basement membrane

The metastatic niche is altered by neuroinflammation

The outcome of brain metastasis is dependent on the interaction that takes place between tumor cells and CNS microenvironment

Astrocytes can enable the growth of brain tropic tumor cell lines in co-culture experiments



Seike T, Clin. Exp Metastasis 2001

Angiogenesis plays a crucial role in tumor growth, metastasis and response to chemotherapy

Complex vascular changes are evident during parenchymal colonization

Depending on the histological type:

Cancer cells grow by forming new blood vessels (angiogenesis)
High level of VEGF-A

Develop by growing along pre-existing blood vessels (valscular co-option)
Low level of VEG-A

Jubb AM, Br. J. Cancer, 2011
Gandhi P.A.,Clin. Camcer Res., 2012

Why chemotherapy usually fails

The BBB prohibits adequate amounts of CT or targeted therapy from reaching the brain mts

In patients without brain metastases, the ratio of trastuzumab in plasma to trastuzumab in cerebrospinal fluid is >300:1

Pestalozzi J Am Soc Clin Oncol, 2000
Stemmler HJ, Oncol, 2008

Why chemotherapy usually fails

Brain mts may result from late development after multiple cycles of CT and can reflect accumulated mutations

To develop brain mts tumor cells acquire must acquire several mutations different from other systemic mts

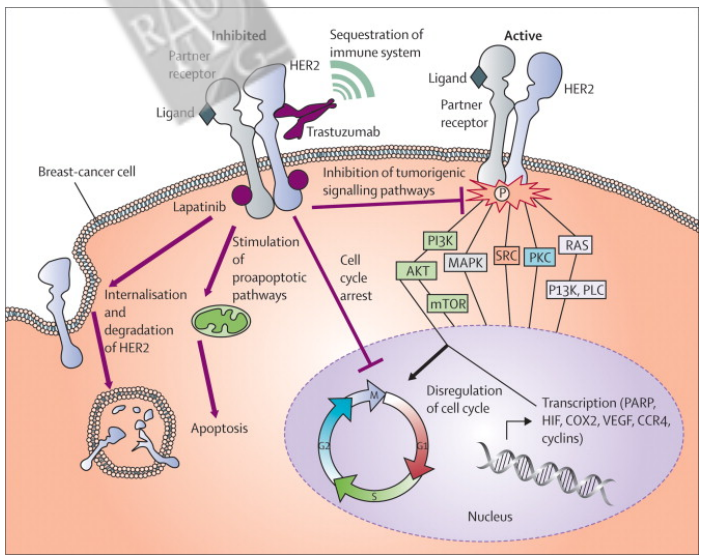
Patients with brain metastases are excluded from clinical trials

Breast Cancer

HER2 is a member of the human EGFR family.

Amplification or over-expression of this oncogene has been shown to play an important role in the development and progression of certain aggressive types of breast cancer

The dual tyrosine kinase inhibitor targeting EGFR and HER2 **Lapatinib** has been developed for pts with breast cancer that have developed resistance to trastuzumab



Mitri Z Chemotherapy Research and Practice, 2012

Erin G. Worral, 2012

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XXX CONGRESSO NAZIONALE AIRB
IX CONGRESSO NAZIONALE AIRO GIOVANI

Clin Cancer Res 2009;15(4) February 15, 2009

Cancer Therapy: Clinical

Multicenter Phase II Study of Lapatinib in Patients with Brain Metastases from HER2-Positive Breast Cancer

Nancy U. Lin,[1] Véronique Diéras,[2] Devchand Paul,[3] Dominique Lossignol,[4] Christos Christodoulou,[5] Hans-Joachim Stemmler,[6] Henri Roché,[7] Minetta C. Liu,[8] Richard Greil,[9] Eva Ciruelos,[10] Sibylle Loibl,[11] Stefania Gori,[12] Andrew Wardley,[13] Denise Yardley,[14] Adam Brufsky,[15] Joanne L. Blum,[16] Stephen D. Rubin,[17] Bernie Dharan,[17] Klaudia Steplewski,[17] Denise Zembryki,[17] Cristina Oliva,[18] Debasish Roychowdhury,[17] Paolo Paoletti[17]

VOLUME 26 · NUMBER 12 · APRIL 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase II Trial of Lapatinib for Brain Metastases in Patients With Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

Nancy U. Lin, Lisa A. Carey, Minetta C. Liu, Jerry Younger, Steven E. Come, Matthew Ewend, Gordon J. Harris, Elizabeth Bullitt, Annick D. Van den Abbeele, John W. Henson, Xiaochun Li, Rebecca Gelman, Harold J. Burstein, Elizabeth Kasparian, David G. Kirsch, Ann Crawford, Fred Hochberg, and Eric P. Winer

Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study

Thomas Bachelot, Gilles Romieu, Mario Campone, Véronique Diéras, Claire Cropet, Florence Dalenc, Marta Jimenez, Emilie Le Rhun, Jean-Yves Pierga, Anthony Gonçalves, Marianne Leheurteur, Julien Domont, Maya Gutierrez, Hervé Curé, Jean-Marc Ferrero, Catherine Labbe-Devilliers

www.thelancet.com/oncology **Published online November 2, 2012** **http://dx.doi.org/10.1016/S1470-2045(12)70432-1**

Single-arm phase 2, open-label, multicentre study

Eligible patients had HER2-positive metastatic breast cancer with brain metastases not previously treated with WBRT capecitabine, or lapatinib.

Tretament was given in 21 day cycles: patients received lapatinib (1250 mg, orally) every day and capecitabine (2000 mg/m², orally) from day 1 to day 14.

The primary endpoint was the proportion of patients with an objective CNS response, defined as a 50% or greater volumetric reduction of CNS lesions in the absence of increased steroid use, progressive neurological symptoms, and progressive extra-CNS disease.

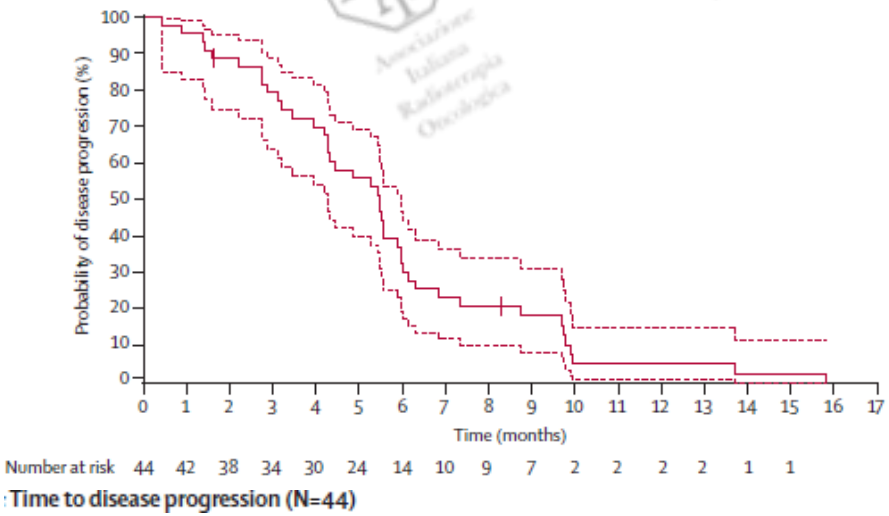
Results:

45 pts with a median follow-up of 21·2 months (range 2 were enrolled·2–27·6)

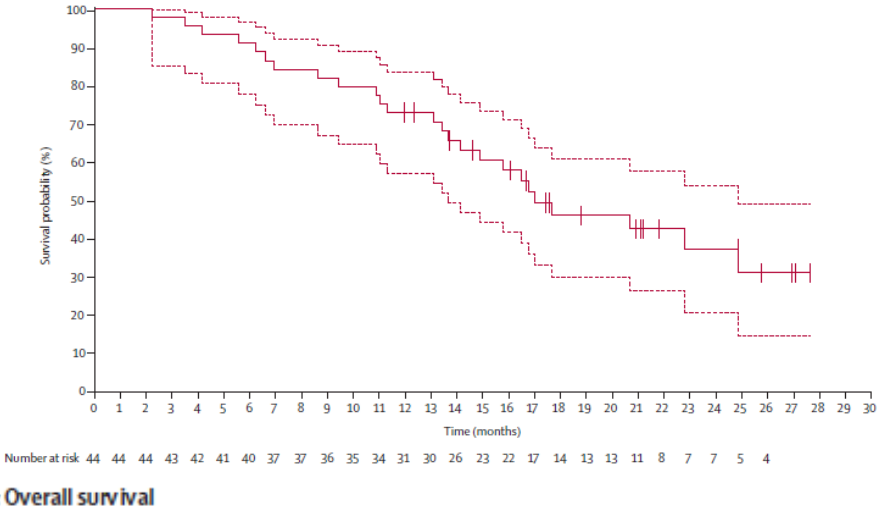
Objective response rate of 65.9 %, with a median time to progression of 5.5 months and a 1-year survival rate >70 %

Median time to WBRT accounted 8.3 months

22 pts (49%) G3 or G4 treatment-related adverse events



Time to disease progression (N=44)



Overall survival

J Natl Cancer Inst 2008;100:1092–1103

Effect of Lapatinib on the Outgrowth of Metastatic Breast Cancer Cells to the Brain

Brunilde Gril, Diane Palmieri, Julie L. Bronder, Jeanne M. Herring, Eleazar Vega-Valle, Lionel Feigenbaum, David J. Liewehr, Seth M. Steinberg, Maria J. Merino, Stephen D. Rubin, Patricia S. Steeg

Breast Cancer Research and Treatment
December 2008, Volume 112, Issue 3, pp 533–543

A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses

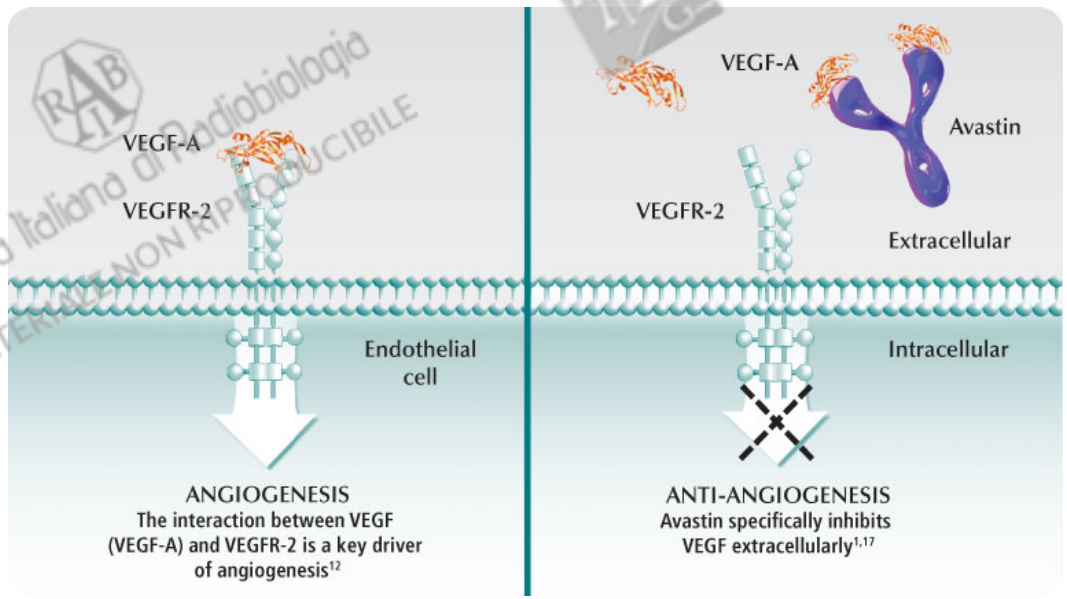
Authors | Authors and affiliations

David Cameron, Michelle Casey, Michael Press, Deborah Lindquist, Tadeusz Pienkowski, C. Gilles Romieu, Stephen Chan, Agnieszka Jagiello-Gruszfeld, Bella Kaufman, John Crown, Arlene Chan, Mario Campone, Patrice Viens, Neville Davidson,

Laboratory and clinical evidence supports the central role of angiogenesis in the progression of breast cancer

VEGF stimulates endothelial proliferation and migration, inhibits endothelial apoptosis, induces proteinases that remodel the extracellular matrix, increases vascular permeability and vasodilatation, and inhibits antigen-presenting dendritic cells

Miller, K., NEGM 2007



The NEW ENGLAND JOURNAL of MEDICINE

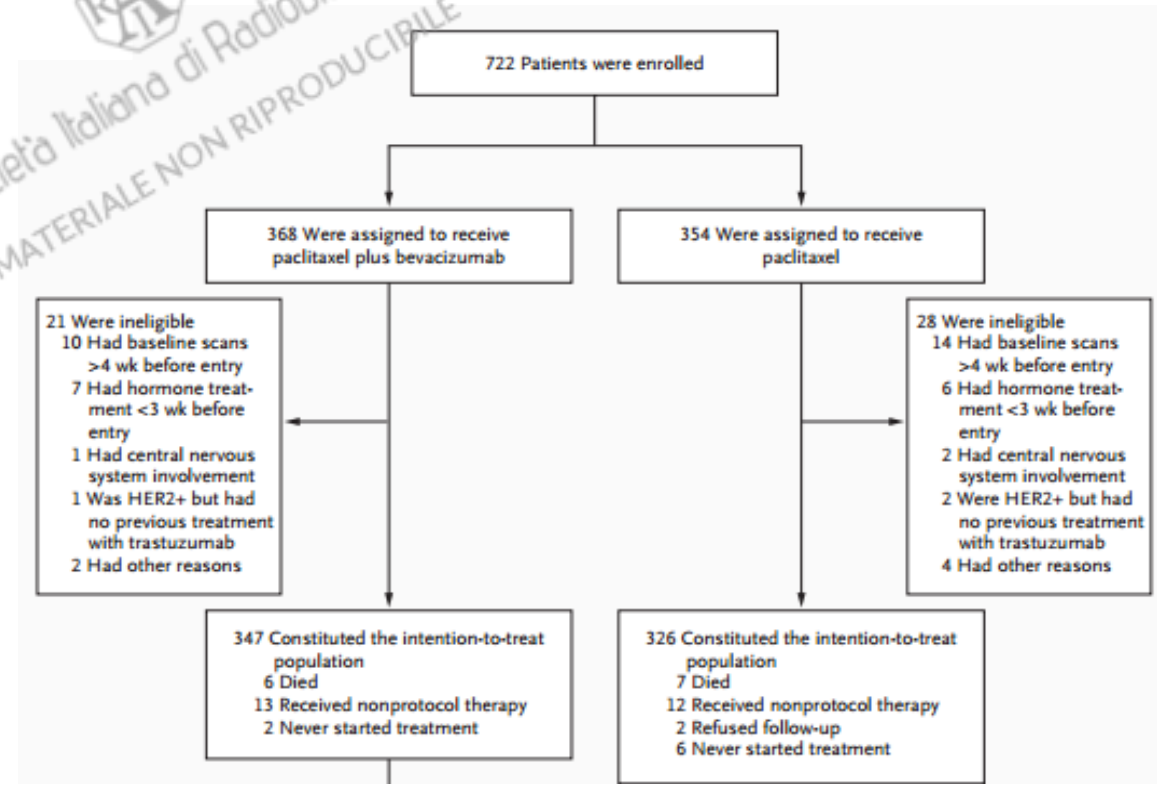
ORIGINAL ARTICLE

Paclitaxel plus Bevacizumab versus Paclitaxel Alone for Metastatic Breast Cancer

Kathy Miller, M.D., Molin Wang, Ph.D., Julie Gralow, M.D., Maura Dickler, M.D., Melody Cobleigh, M.D., Edith A. Perez, M.D., Tamara Shenkier, M.D., David Cella, Ph.D., and Nancy E. Davidson, M.D.

From December 2001 to May 2004 722 patients were enrolled

The primary end point was progression-free survival; overall survival was a secondary end point



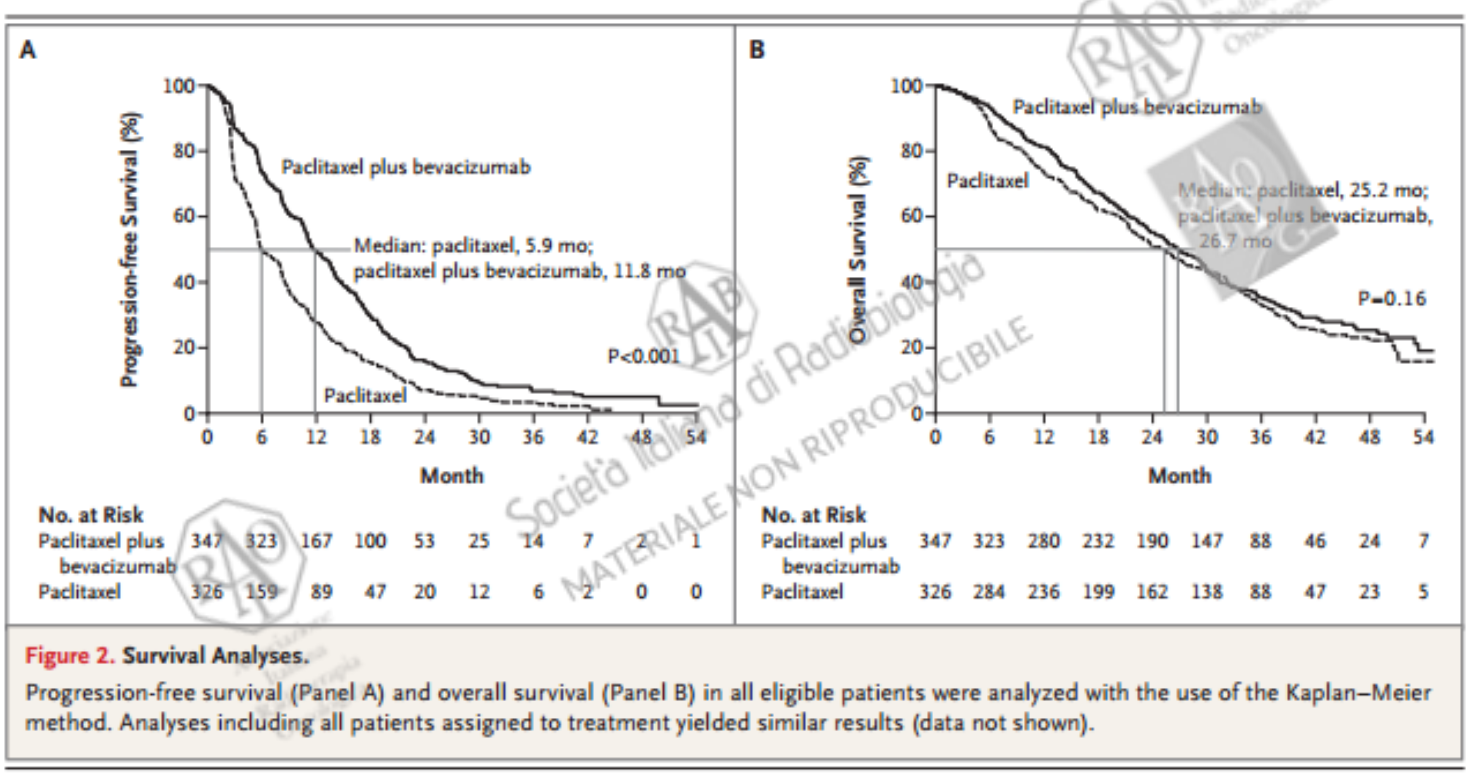
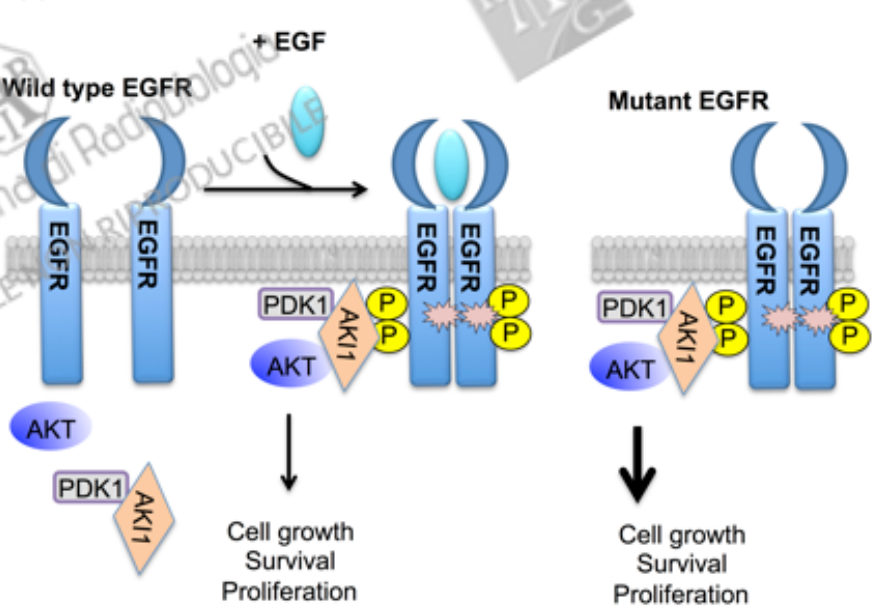


Figure 2. Survival Analyses.
Progression-free survival (Panel A) and overall survival (Panel B) in all eligible patients were analyzed with the use of the Kaplan–Meier method. Analyses including all patients assigned to treatment yielded similar results (data not shown).

Conclusions: Initial therapy of metastatic breast cancer with paclitaxel plus bevacizumab prolongs progression-free survival, but not overall survival, as compared with paclitaxel alone

The use of drugs targeting the proteins of mutated **EGFR** and **ALK** genes has become standard of care in the systemic treatment of metastatic NSCLC (gefitinib, erlotinib, afatinib)

The mutation status of tumors is usually derived from biopsies obtained at extracranial sites, and thus, does not necessarily guarantee a mutation in the sub-clones within the brain



Xiaoling S., Onco Reviews, 2015

Tumor Biology
March 2014, Volume 35, Issue 3, pp 2437–2444

EGFR mutation status and its impact on survival of Chinese non-small cell lung cancer patients with brain metastases

Authors | Authors and affiliations

Dongdong Luo, Xin Ye, Zheng Hu, Kaiwen Peng, Ye Song, Xiaolu Yin, Guanshan Zhu, Qunsheng Ji, Yuping Peng

136 NSCLC patients with resected BM, in which an EGFR mutation was identified in 57% of the BM, found a con- cordance rate of 93.3% in the EGFR mutation status between the primary tumor and BM

Neuro-Oncology Advance Access published July 13, 2010

Neuro-Oncology
doi:10.1093/neuonc/noq076

NEURO-ONCOLOGY

EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer

April F. Eichler, Kristopher T. Kahle, Daphne L. Wang, Victoria A. Joshi, Henning Willers, Jeffrey A. Engelman, Thomas J. Lynch, and Lecia V. Sequist

Massachusetts General Hospital Cancer Center (A.F.E., D.L.W., V.A.J., H.W., J.A.E., L.V.S.); Pappas Center for Neuro-Oncology (A.F.E., D.L.W.); Center for Thoracic Cancers (H.W., J.A.E., L.V.S.); and Massachusetts General Hospital Departments of Pathology (V.A.J.); Radiation Oncology (H.W.); Neurosurgery (K.T.K.); Harvard Medical School, Boston, Massachusetts (A.F.E., K.T.K., V.A.J., J.A.E., L.V.S.); Yale Comprehensive Cancer Center, Yale Medical School, New Haven, Connecticut (T.J.L.)

In this same cohort of patients, the median OS was 24.5months in the EGFR mutation group, compared to 15months in thewild-type group. This finding is consistentwith other studies identifying EGFR mutation status as a positive prognostic factor among patients with BM

Eur Respir J 2011; 37: 624–631
DOI: 10.1183/09031936.00195609

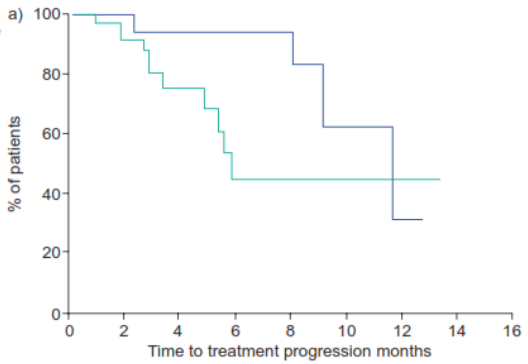
Brain metastases from lung cancer responding to erlotinib: the importance of *EGFR* mutation

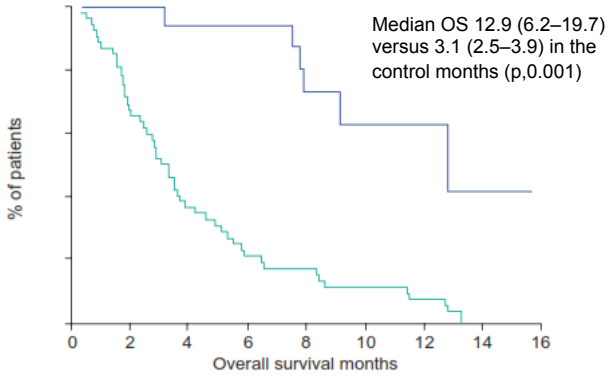
R. Porta, J.M. Sánchez-Torres, L. Paz-Ares, B. Massutí, N. Reguart, C. Mayo, P. Lianes, C. Queralt, V. Guillem, P. Salinas, S. Catot, D. Isla, A. Pradas, A. Gurpide, J. de Castro, E. Polo, T. Puig, M. Tarón, R. Colomer and R. Rosell

Retrospective analysis of patients previously treated with erlotinib (n = 69)

Time to progression within the brain :11.7 months in patients with EGFR mutations compared with 5.8 months in those whose tumors were either EGFR wild type or unassessed (p<0.05)

Only 16% of patients with EGFR mutations had received WBRT versus
85% of those in the control group.





Annals of Oncology

original articles

Annals of Oncology 24: 993–999, 2013
doi:10.1093/annonc/mds529
Published online 4 November 2012

Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG–0803)†

Y.-L. Wu[1*], C. Zhou[2], Y. Cheng[3], S. Lu[4], G.-Y. Chen[5], C. Huang[6], Y.-S. Huang[1], H.-H. Yan[1], S. Ren[2], Y. Liu[3] & J.-J. Yang[1]

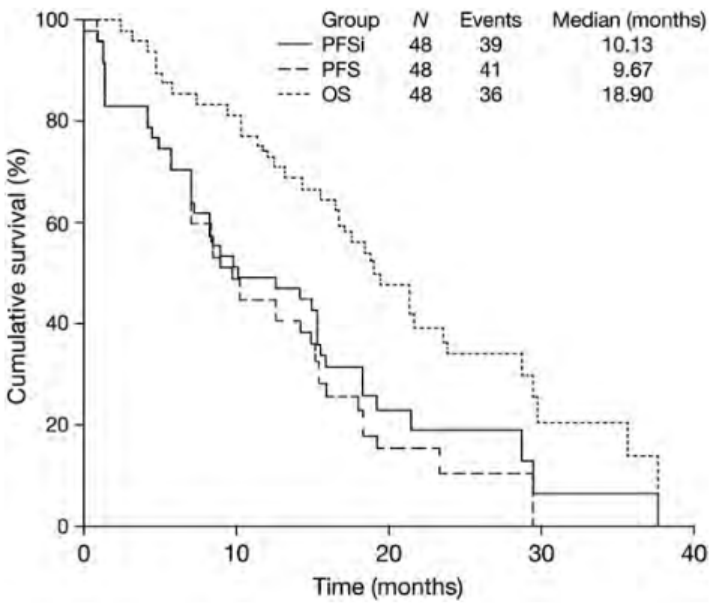
[1]*Guangdong Lung Cancer Institute, Guangdong General Hospital and Guandong Academy of Medical Sciences, Guangzhou;* [2]*Shanghai Pulmonary Hospital, Shanghai;* [3]*Jilin Tumor Hospital, Changchun;* [4]*Shanghai Chest Hospital affiliated to Shanghai JiaoTong University, Shanghai;* [5]*The Affiliated Tumor Hospital of Harbin Medical University, Harbin;* [6]*Fujian Tumor Hospital, Fuzhou, China*

Prospective single-arm trial evaluated the role of second-line erlotinib in Asian patients (*n*=48) with metastatic NSCLC and asymptomatic BM.

EGFR status: 17% positive, 31% wild type, 52% of unknown.

Intracranial PFS was 10.1months in the overall population

Among patients with *EGFR* mutations, PFS was 15.2months, which was significantly longer than the 4.4 months in patients with *EGFR* wild-type tumors (*p*=0.02).

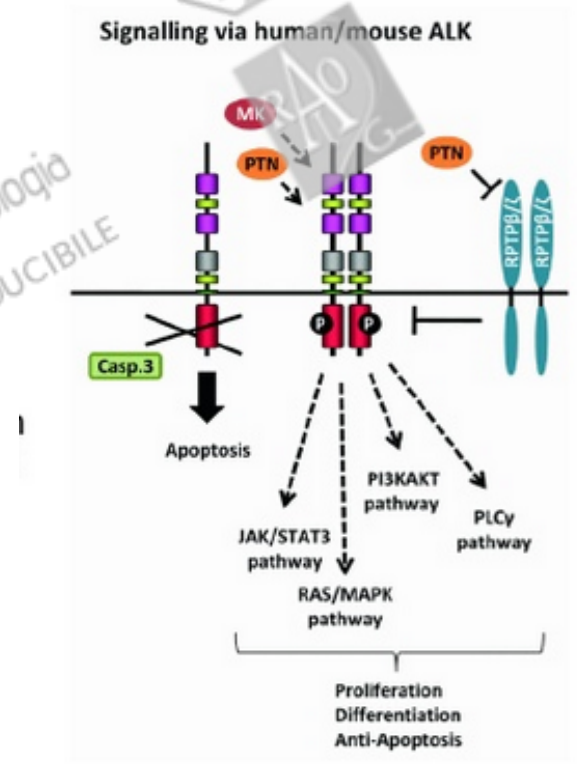


The ***ALK*** gene encodes a receptor tyrosine kinase that is activated in a subset of patients with NSCLC and other tumors

ALK inhibitors such as **crizotinib** have shown to be effective in tumor response and disease control

Despite an initial response, many patients with *ALK*-positive NSCLC will eventually progress, with the CNS being a common site of initial disease progression

Shaw AT, N Engl J Med, 2013
Shaw AT, J Clin Oncol, 2009
Kim YH, Biomed Rep, 2013



Biochemical Journal (2009) Volume **420**, 345-361

(*J Thorac Oncol.* 2012;7: 1807–1814)

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

Andrew J. Weickhardt, MBBS, DmedSc, Benjamin Scheier, MD,* Joseph Malachy Burke, MD,* Gregory Gan, MD,‡ Xian Lu, MSc,‡ Paul A. Bunn, Jr., MD,* Dara L. Aisner, MD, PhD,§ Laurie E. Gaspar, MD, MBA,‡ Brian D. Kavanagh, MD, MPH,‡ Robert C. Doebele, MD, PhD,* and D. Ross Camidge, MD, PhD**

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 368;25 NEJM.ORG JUNE 20, 2013
ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D., Tommaso De Pas, M.D., Benjamin Besse, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Fiona Blackhall, M.D., Ph.D., Yi-Long Wu, M.D., Michael Thomas, M.D., Kenneth J. O'Byrne, M.D., Denis Moro-Sibilot, M.D., D. Ross Camidge, M.D., Ph.D., Tony Mok, M.D., Vera Hirsh, M.D., Gregory J. Riely, M.D., Ph.D., Shrividya Iyer, Ph.D., Vanessa Tassell, B.S., Anna Polli, B.S., Keith D. Wilner, Ph.D., and Pasi A. Jänne, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

Crizotinib has been considered to have limited activity in BM compared with other sites of metastasis because of poor penetration across the BBB

Overall incidence of BM in patients with *ALK*-positive NSCLC is high, suggesting that the higher rate of CNS progression compared with systemic progression could result from a low plasma to CSF ratio

This suggests that approaches to increase the concentration of crizotinib within the CNS or use of other ALK inhibitors with greater CSF penetration may have therapeutic potential

In a retrospective analysis of patients with *ALK*-positive NSCLC receiving crizotinib treatment in phase 1 and 2 trials, 46% of patients progressed first in the CNS

Crizotinib was 23 times more plasma versus CSF ng/mL, evident in several recent trials in which 35% to 50% of enrolled patients had stable or asymptomatic BM

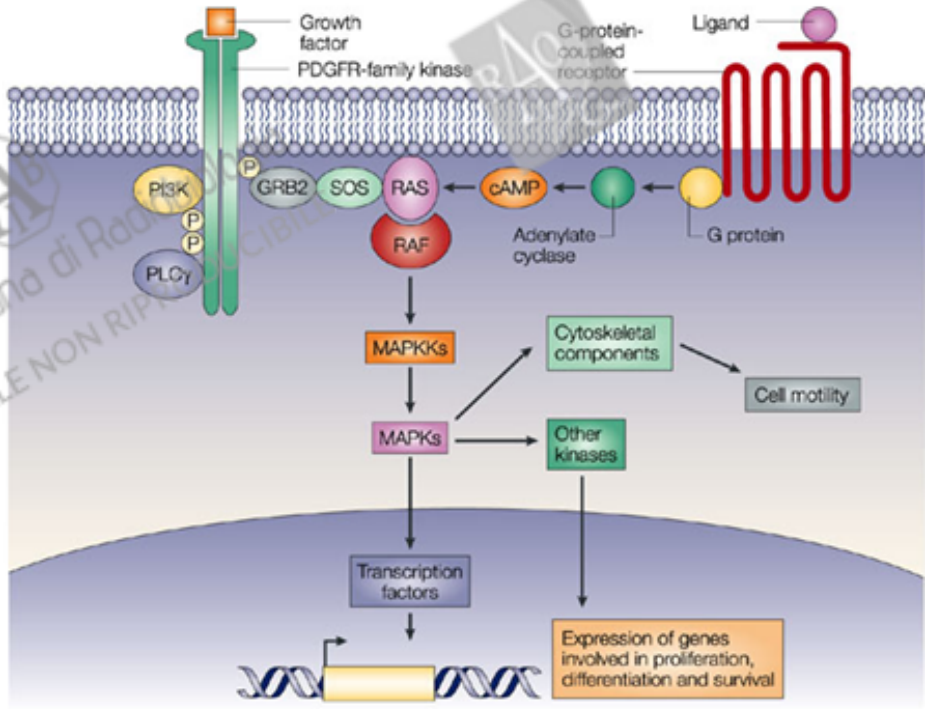
This has created the need for a greater understanding of both the CNS activity of currently approved ALK inhibitors and the potential of those currently in development.

BRAF is a human gene that makes a protein called B-Raf.

The B-Raf protein is involved in sending signals inside cells which are involved in directing cell growth

Braf V600E mutations are associate with increased sensitivity with B-RAF

Drugs that treat cancers driven by *BRAF* mutations have been developed. Two of these drugs, **vemurafenib**, and **dabrafenib** are approved by FDA for treatment of late-stage melanoma



Corcoran RB SJ, Potential therapeutic strategies to overcome acquired resistance to BRAF or MEK inhibitors in BRAF mutant cancers. Oncotarget. 2011;4:336-46

Gerhard K, Biochemistry of Signal Transduction and Regulation, 2008

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RAF Inhibitor Dabrafenib (GSK2118436) is Active in Melanoma Brain Metastases, Multiple BRAF Genotypes and Diverse Cancers

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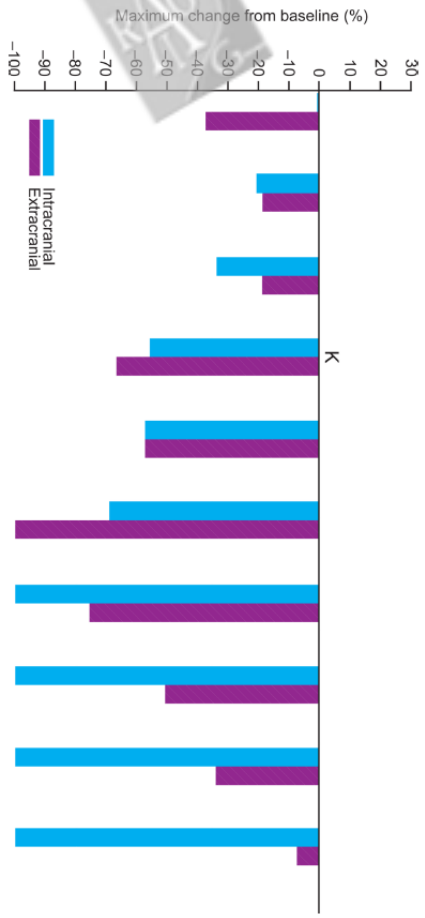


Nine of the ten patients (90%) achieved a decrease in brain lesions, and four of ten patients achieved complete resolution of all brain lesions

All patients were alive at 5 months, and two survived beyond 12 months.

Significant progresses have been made in the treatment of selected malignancies with immune modulating antibodies

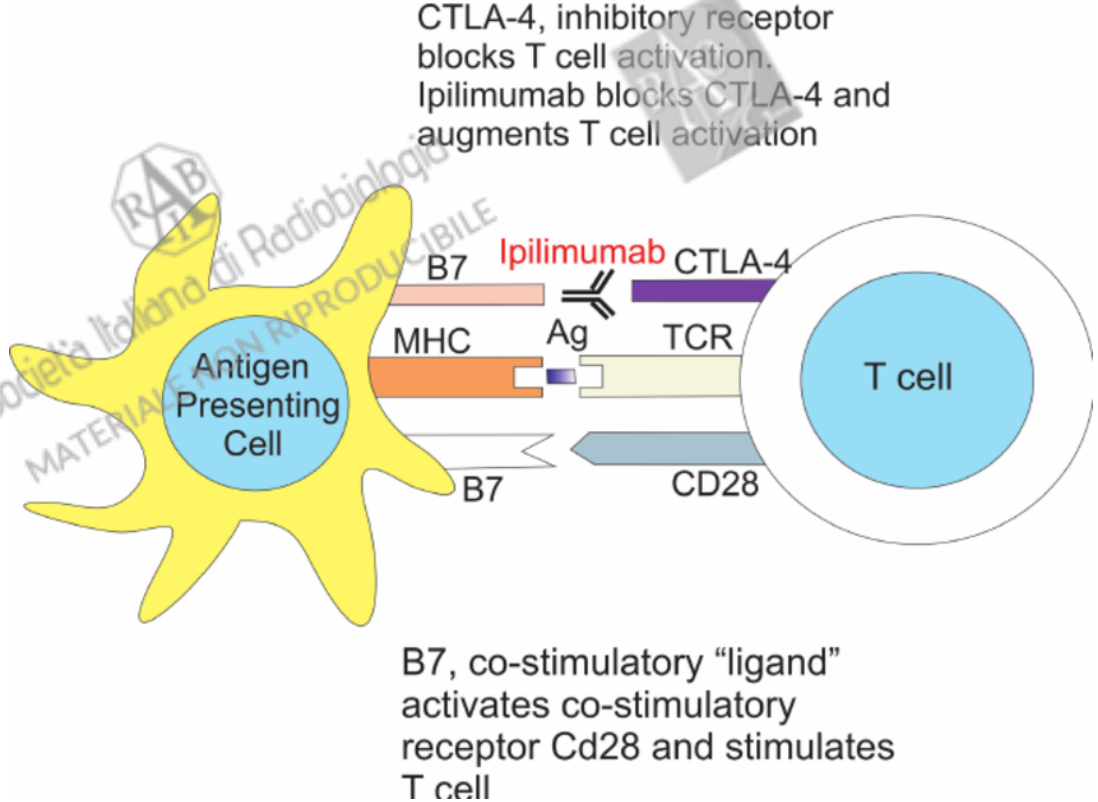
Phase III trial of anti-CTLA-4 and anti-PD-1 in melanoma, RCC and NSCLC showed improved OS compared to standard treatment

Blockade of CTLA-4 (ipilimumab, and trelimumab), PD-1 (nivolumab, pembrolizumab, pidilizumab and others) and PD-L1 (durvalimumab, atezolizumabes andothers) can produce durable response in pts with metastatic cancer

These drugs need to be assessed for efficacy in active brain metastases

CD28 and cytotoxic T-lymphocyte antigen 4 (CTLA-4) play important roles in the regulation of immune activation and tolerance.

Both clinical and preclinical data indicate that CTLA-4 blockade results in direct activation of CD4+ and CD8+ effector cells, and anti–CTLA-4 monoclonal antibody therapy has shown promise in a number of cancers, particularly melanoma.



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Lancet Oncol 2012; 13: 459–65

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

Between July 2008 and June 2009 72 pts with melanoma and brain mts were enrolled

Cohort A: neurologically asymptomatic and not receiving corticosteroid
Cohort B: symptomatic and on a stable dose corticosteroid

Ipilimumab:

four doses of 10 mg/kg one every 3 weeks → 10 mg/kg one every 12 weeks

Clinical stable pts at weeks 24

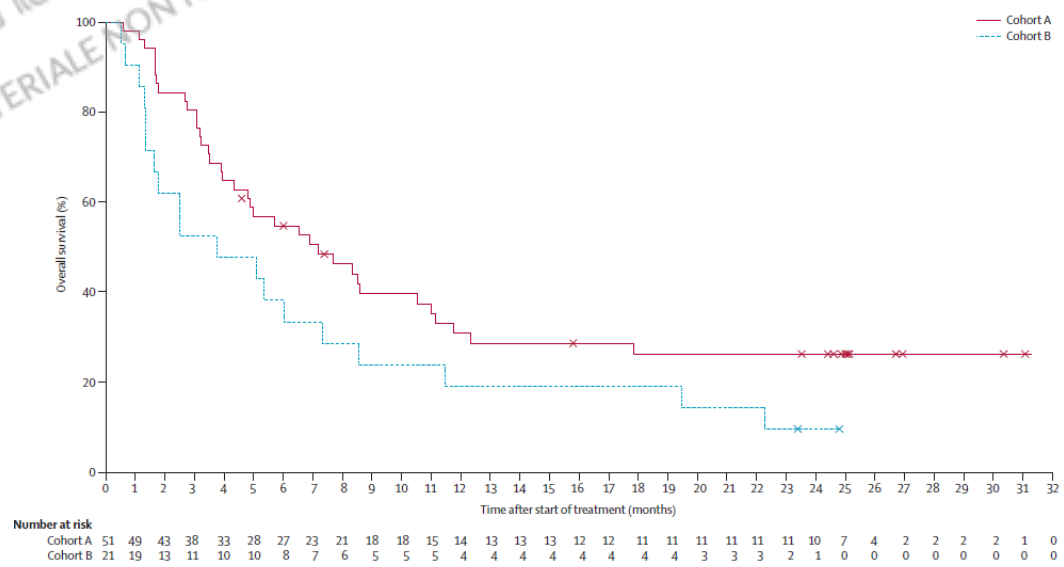
Lancet Oncol 2012; 13: 459–65

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

Primary endpoint:proportion of pts with disease control after 12 weeks

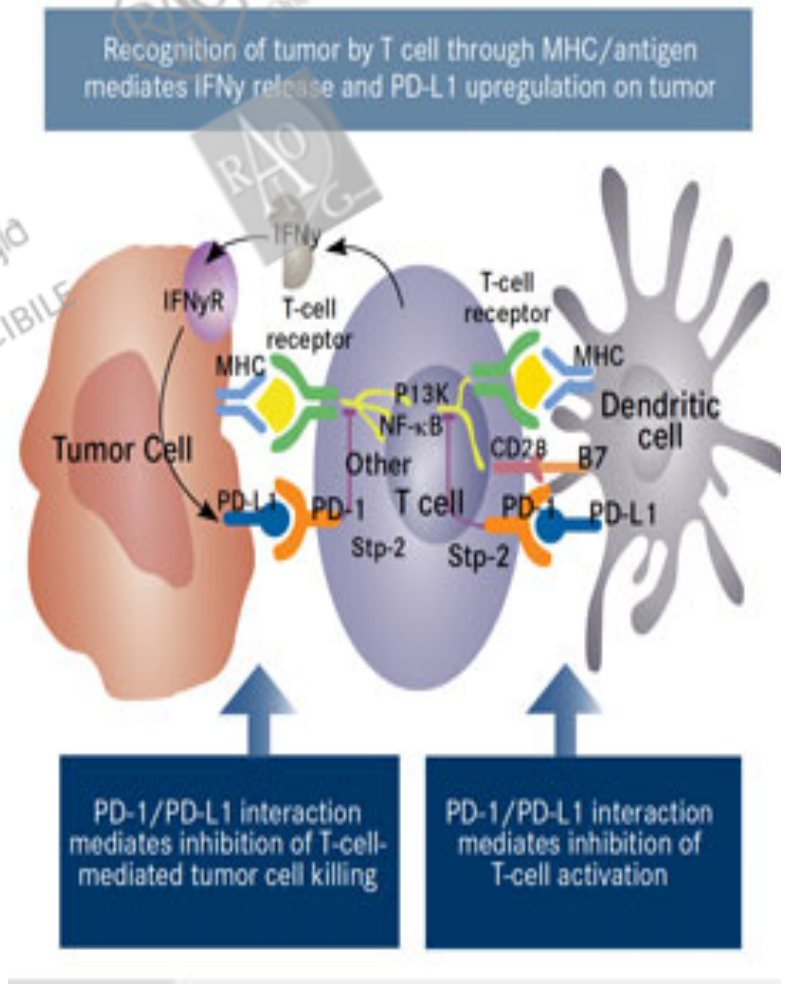
Results: 36 participants in cohort A and 19 in cohort B died.
Median **OS** was 7·0 months (95% CI 4·1–10·8) in cohort A and 3·7 months (1·6–7·3) in cohort B.
Cohort A:
6-**month** survival rate: 55% (95% CI 41–68)
12-month:31% (18–44)
24-month:26% (14–39)



The binding of PD-L1 to PD-1 generates a net immunosuppressive effect and allows the tumor to evade immune destruction

PD-L1 is expressed on the surface of multiple tumors and is likely involved in tumor induced immune evasion and the disparate clinical outcomes (**melanoma**, **renal cell carcinoma**, **lung cancers**, **cancers of the head and neck**, **gastrointestinal malignancies**, **bladder cancer**, **ovarian cancer**, and **hematological malignancies)**

Anti-PD-1 agents (**nivolumab, pembrolizumab and pidilizumab**) are humanized monoclonal antibodies that bind the PD-1 receptor. They prevent the engagement of PD-1 to its ligand on the tumor cells (PD-L1 and PD-L2) thereby asserting its antitumor activity.



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Società Italiana di Radiobiologia

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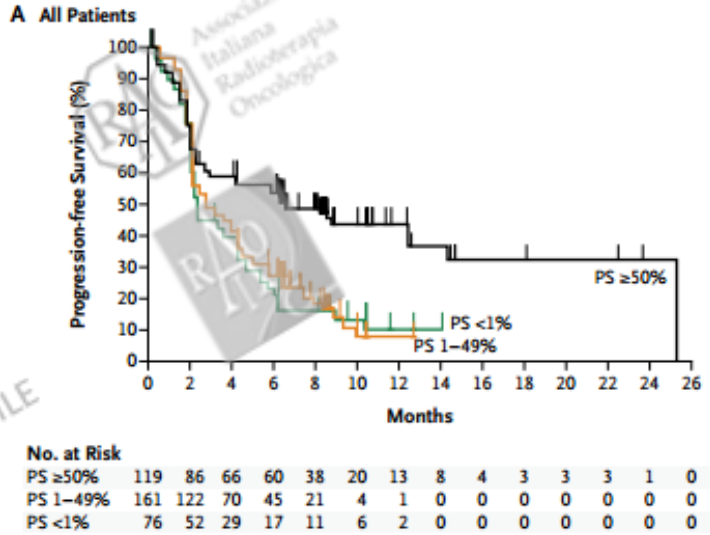
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2015;372:2018-28.

ORIGINAL ARTICLE

Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D., Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D., Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D., Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D., Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D., Jared K. Lunceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D., Charlotte Roach, B.S., Kenneth Emancipator, M.D., and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators*



Cancer Biol Med 2016. doi: 10.20892/j.issn.2095-3941.2016.0009

OPEN ACCESS

REVIEW

Programmed cell death ligand-1 (PD-L1) expression by immunohistochemistry: could it be predictive and/or prognostic in non-small cell lung cancer?

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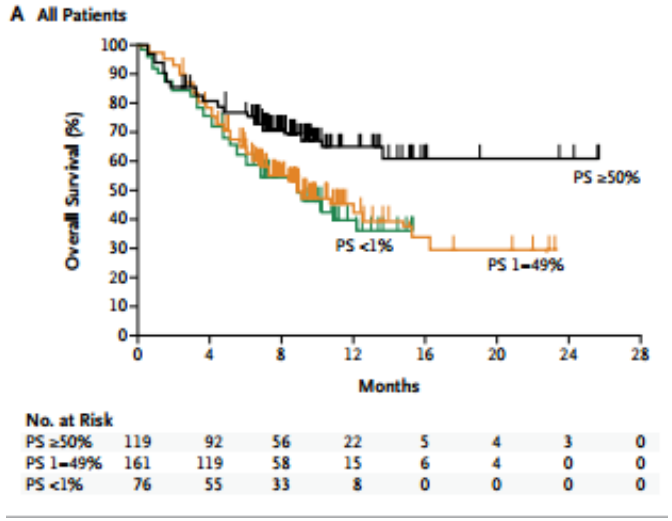
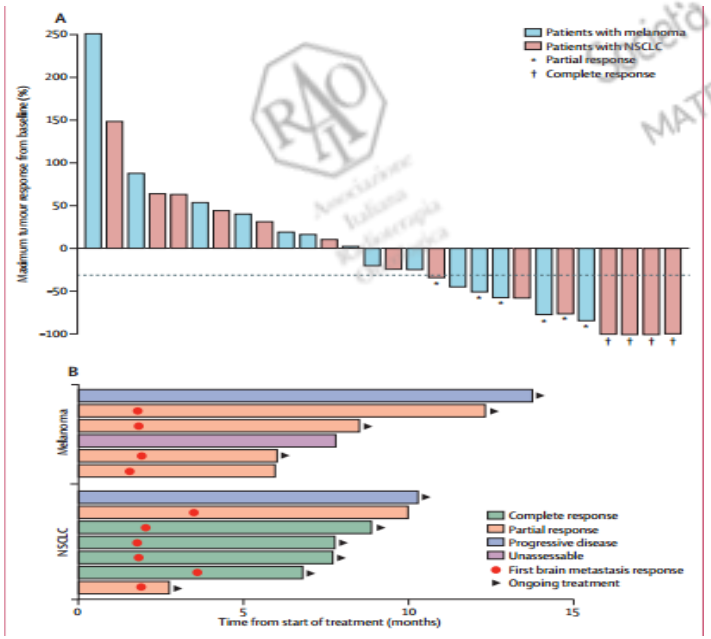


Lancet Oncol 2016; 17: 976–83

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial

Sarah B Goldberg, Scott N Gettinger, Amit Mahajan, Anne C Chiang, Roy S Herbst, Mario Sznol, Apostolos John Tsiouris, Justine Cohen, Alexander Vortmeyer, Lucia Jilaveanu, James Yu, Upendra Hegde, Stephanie Speaker, Matthew Madura, Amanda Ralabate, Angel Rivera, Elin Rowen, Heather Gerrish, Xiaopan Yao, Veronica Chiang, Harriet M Kluger



metastasis before enrolment was required for melanoma patients; use of archival tissue was allowed. Tumour PD-L1 positivity was required for enrolment of NSCLC patients only. We excluded patients with neurological symptoms attributable to brain metastases or who required cortico-steroids to control neurological symptoms or perilesional

Conclusions

Before taking into account a molecular targeted therapy the target must be validated

Immunotherapy may be the winning weapon in the treatment of several cancers, we await for the results of ongoing studies