EUROPEAN LUNG CANCER
CONFERENCE 2016

Oligometastatic NSCLC with driver mutations: guidelines and practical application

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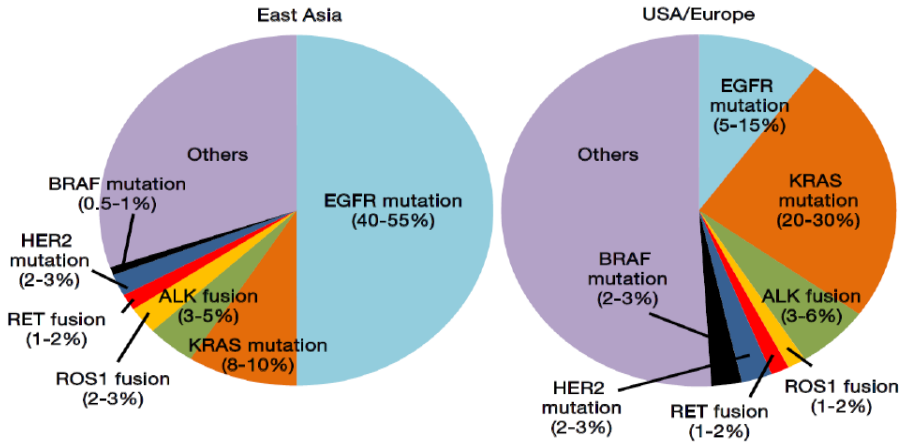
DISCLOSURE SLIDE

Consultancy/advisory role for:

Roche, Pfizer, AstraZeneca, BMS

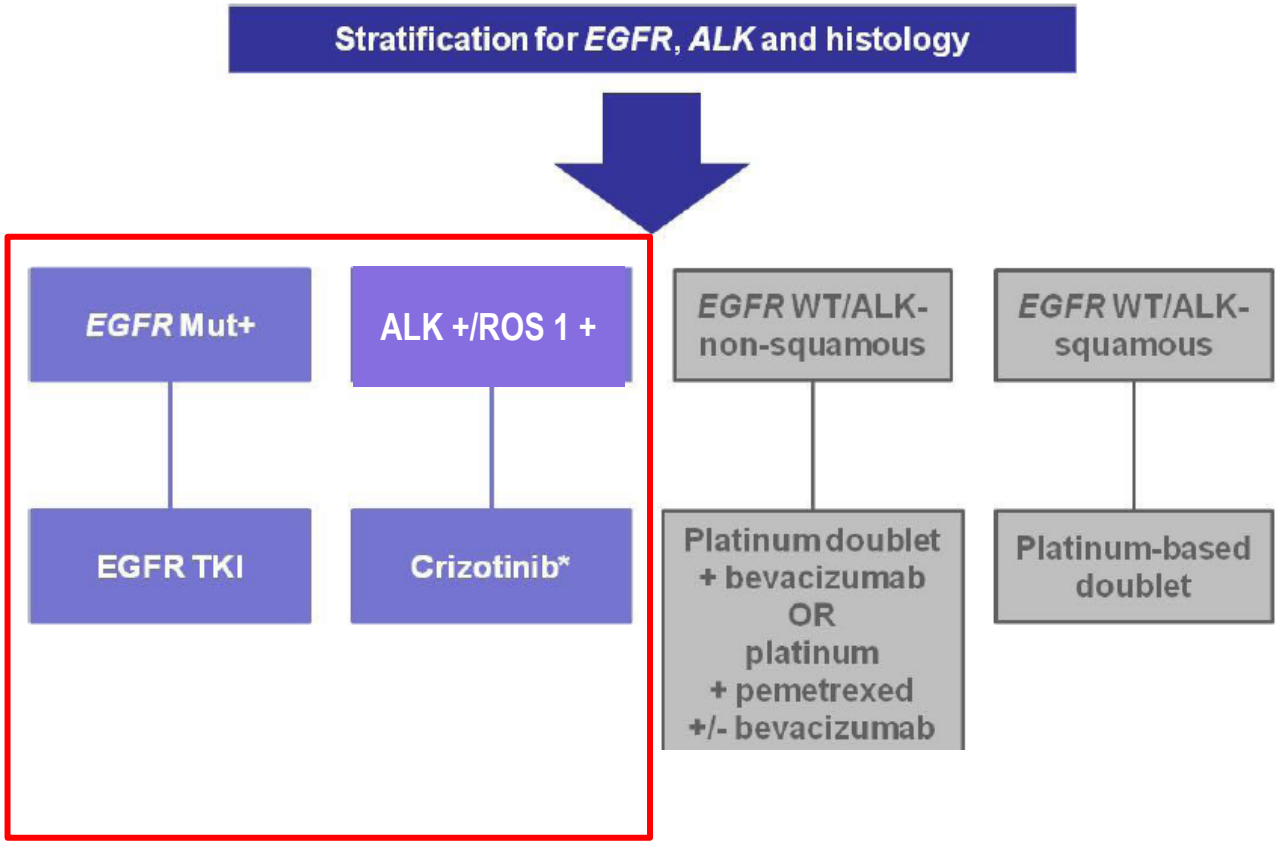
Driver oncogenes in NSCLC



- Certain tumours arise as a result of aberrant activation of a single oncogene and become dependent on this activation
- Identification of druggable oncogenic drivers creates the potential for highly active therapeutic interventions

KohnoTetal.,Transl Lung CancerRes.2015

First-line therapy for metastatic NSCLC with driver oncogene



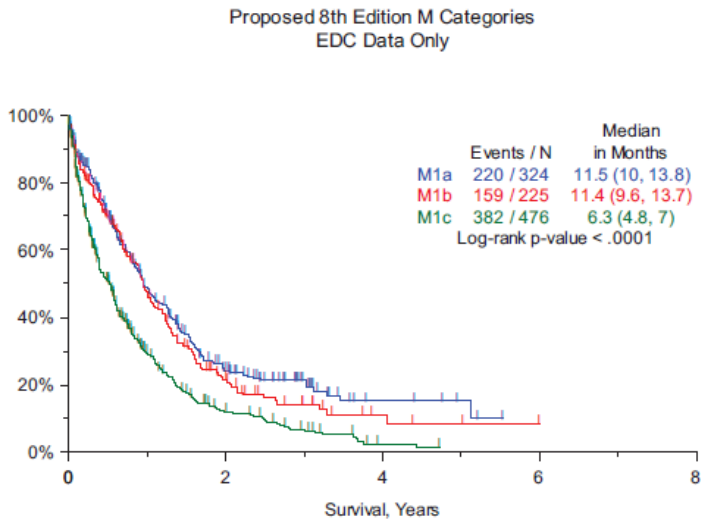
Advanced NSCLC“oligometastasis”—Definition

- Hellman and Weichselbaum first proposed the idea of an oligometastatic state in 1995[1]
  - They suggested that for many cancers a few metastases exist at first, before the malignant cells acquire widespread metastatic potential
  - The number and site of metastatic tumors are limited.
  - Not limited to single organ

1. S. Hellman and R. R. Weichselbaum, “Oligometastases,” *JCO*, vol. 13, no. 1, pp. 8–10, 1995

The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer

M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d]
M1b	**Single extrathoracic metastasis[e]**
M1c	**Multiple extrathoracic metastases in one or more organs**



two M1 categories are sufficiently similar to justify their inclusion in a single stage grouping, the committee believed that it would be useful to retain the separate M categories M1a and M1b for future data collection and analysis because some patients with oligometastatic disease are now receiving more aggressive local therapy in addition to systemic treatment. The more common situation involving multiple metastatic deposits, usually in more than one organ, will now be classified as M1c and staged as IVB.

Goldstraw P , et al. J Thorac Oncol.2016 Jan;11(1):39-51

clinical practice guidelines

Annals of Oncology 25 (Supplement 3): iii27–iii39, 2014
doi:10.1093/annonc/mdu199
Published online 11 August 2014

Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Reck[1,2], S. Popat[3,4], N. Reinmuth[1,2], D. De Ruysscher[5], K. M. Kerr[6], S. Peters[7] & on behalf of the ESMO Guidelines Working Group*

[1]Department of Thoracic Oncology, LungenClinic, Grosshansdorf; [2]Member of the German Center for Lung Research (DZL), Germany; [3]Royal Marsden Hospital NHS Foundation Trust, London; [4]Royal Marsden Hospital NHS Foundation Trust, Surrey, UK; [5]Department of Radiation Oncology, University Hospitals Leuven/ KU Leuven, Leuven, Belgium; [6]Department of Pathology, Aberdeen Royal Infirmary and Aberdeen University Medical School, Aberdeen, UK; [7]Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

treatment of oligometastatic NSCLC

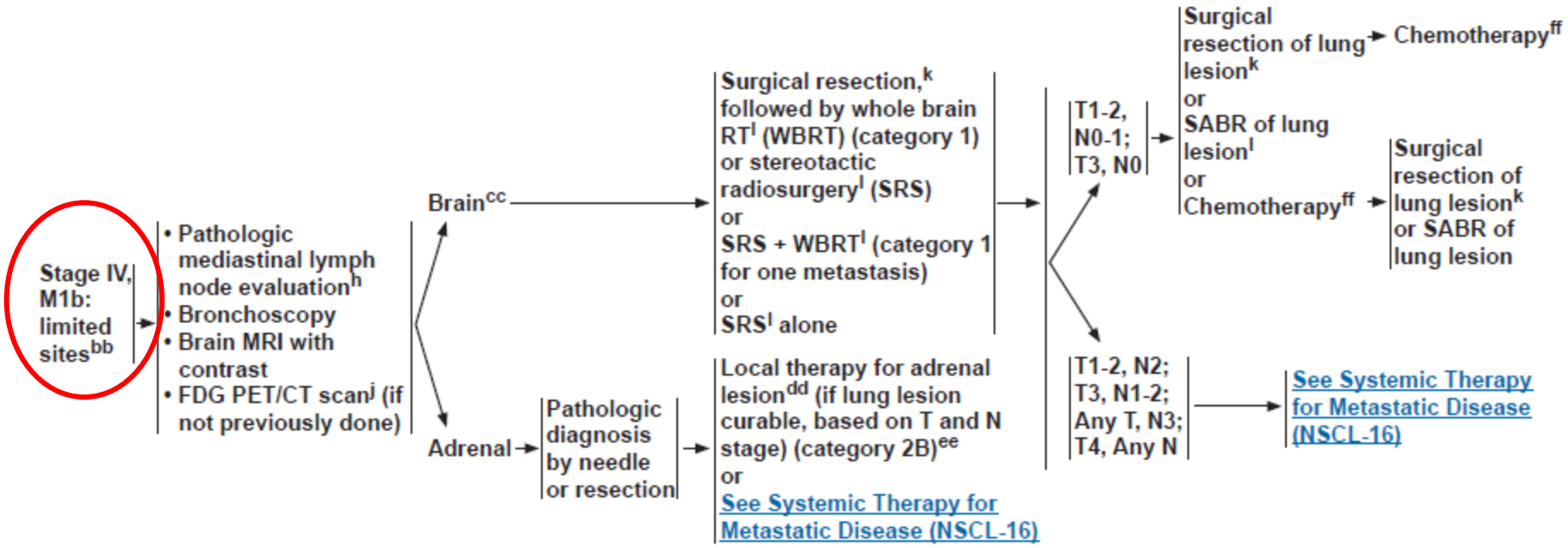
Oligometastases are mostly defined as at maximum five metastatic lesions in the body. Oligometastases can be either synchronous, when diagnosed within 1 month before or after the primary tumour was identified, or metachronous when they appear after treatment of the primary. The biology and prognosis related to synchronous and metachronous oligometastases may differ.

Radical local therapy with high-dose radiotherapy or surgery is appealing, but these patients should also be preferentially included in prospective trials.

M. Reck, et al. Ann Oncol. 2014 Sep;25 Suppl 3:iii27-39

NCCN Guidelines Version 4.2016
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion



[h]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[k]See Principles of Surgical Therapy (NSCL-B).
[l]See Principles of Radiation Therapy (NSCL-C).
[bb]Aggressive local therapy may be appropriate for selected patients with limited-site oligometastatic disease.
[cc]See NCCN Guidelines for Central Nervous System Cancers.
[dd]May include adrenalectomy or RT (including SABR).
[ee]Patients with N2 disease have a poor prognosis and systemic therapy should be considered.
[ff]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

management of widespread distant metastases is described in another section (see *Treatment of Recurrences and Distant Metastases* in this Discussion and *Systemic Therapy for Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Pleural or pericardial effusion is a criterion for stage IV, M1a disease. T4 with pleural effusion is classified as stage IV, M1a (see Table 3 in *Staging* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[105] Although pleural effusions are malignant in 90% to 95% of patients, they may be related to obstructive pneumonitis, atelectasis, lymphatic or venous obstruction, or a pulmonary embolus. Therefore, pathologic confirmation of a malignant effusion by using thoracentesis or pericardiocentesis is recommended. In certain cases where thoracentesis is inconclusive, metastases and, thus, spare some patients from unnecessary surgery. However, positive FDG PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If the FDG PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. Patients with limited oligometastatic disease (eg, single brain or adrenal metastasis) and otherwise limited disease in the chest may benefit from aggressive local therapy to both the primary chest and metastatic sites.[668,669] Aggressive local therapy may comprise surgery or definitive RT including SABR to each site, and may be preceded or followed by chemotherapy. Recent data suggest that erlotinib combined with SABR or SRS may also be useful.[430]

Tumor Heterogeneity

- Targeted therapy has a good effect in advanced NSCLC patients with driven gene mutations
- But taking into account the heterogeneity of tumors, targeted drugs for cancer patients based on the efficacy of targeted therapy in combination local treatment may be a better choice

Synchronous vs Metachronous Oligometastatic Disease

- Synchronous
  - Diagnosed within 1 month before or after the primary tumour was identified
- Metachronous
  - Appear after treatment of the primary.
- The biology and prognosis related to synchronous and metachronous oligometastases may differ

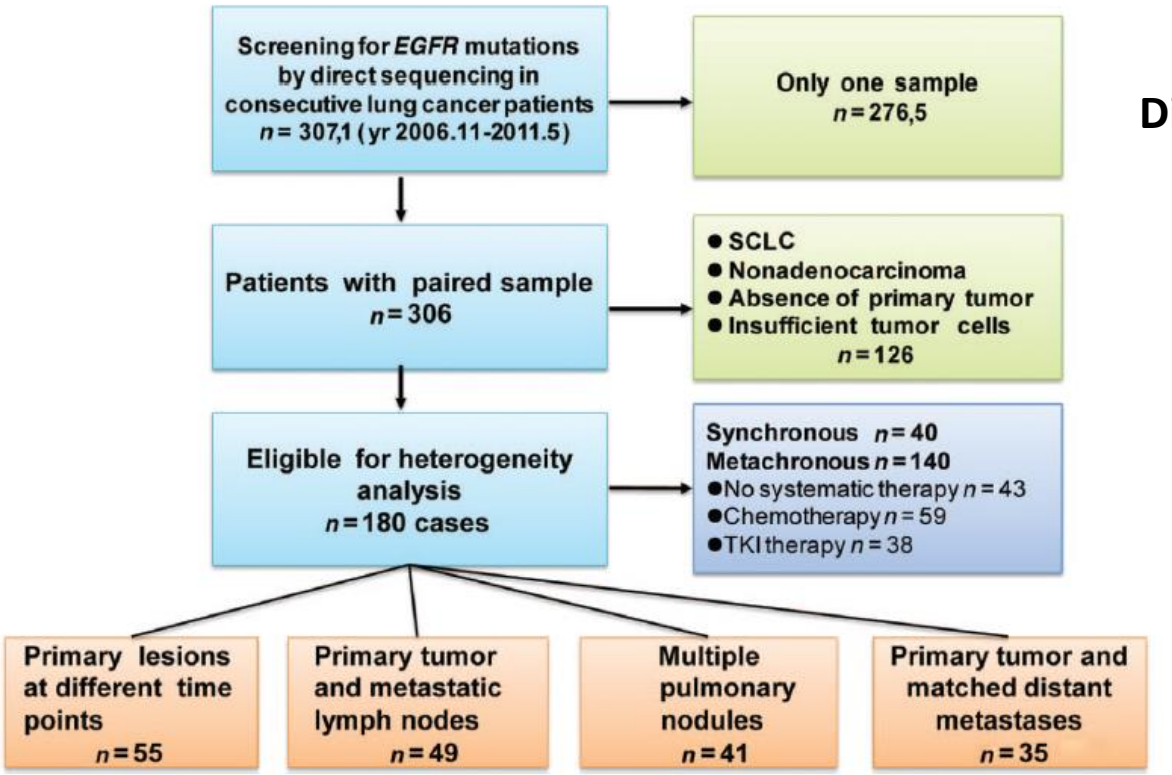
M. Reck, et al. Ann Oncol. 2014 Sep;25 Suppl 3:iii27-39

The Oncologist

Lung Cancer

EGFR Mutation Heterogeneity and the Mixed Response to EGFR Tyrosine Kinase Inhibitors of Lung Adenocarcinomas

Zhi-Yong Chen,[a] Wen-Zhao Zhong,[a] Xu-Chao Zhang,[a] Jian Su,[a] Xue-Ning Yang,[a] Zhi-Hong Chen,[a] Jin-Ji Yang,[a] Qing Zhou,[a] Hong-Hong Yan,[a] She-Juan An,[a] Hua-Jun Chen,[a] Ben-Yuan Jiang,[a] Tony S. Mok,[b] Yi-Long Wu[a]



Discordance rates:

- **metachronous :15.7% (22 of 140)**
- **synchronous: 7.5% (3of 40)**

ZHI-YONG CHEN, et al. The Oncologist 2012;17:000–000

Synchronous vs Metachronous Oligometastatic Disease

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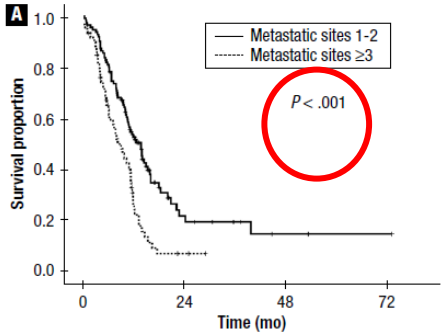
M. Reck, et al. Ann Oncol. 2014 Sep;25 Suppl 3:iii27-39

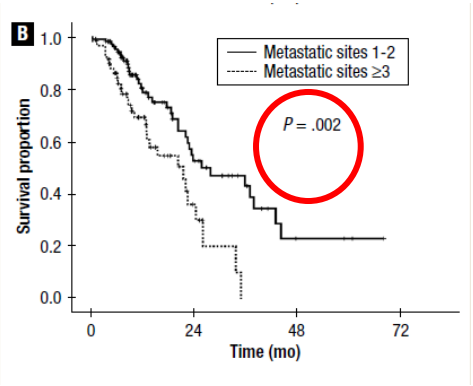
Tumor Burden is Predictive of Survival in Patients With Non–Small-Cell Lung Cancer and With Activating Epidermal Growth Factor Receptor Mutations Who Receive Gefitinib

Jin Hyun Park,[1] Tae Min Kim,[1,2] Bhumsuk Keam,[1,2] Yoon Kyung Jeon,[3] Se-Hoon Lee,[1,2] Dong-Wan Kim,[1,2] Doo Hyun Chung,[3] Young Tae Kim,[4] Young Whan Kim,[1] Dae Seog Heo[1,2]

- 170 patients with NSCLC and with EGFR mutations received gefitinib as a first-line (n=50) and a second-line or more (n=120) treatment
- The number of metastatic sites was at least 3, significantly reduced survival was observed (median PFS 8.5 vs. 14.0 months, *P< 0 .001; median OS 21.4 vs. 25.6 months, P=0 .002).*



PFS



OS

Jin Hyun Park , et al. *Clinical Lung Cancer, 2013 ,Vol. 14, No. 4, 383-9*

VOLUME 34 · NUMBER 2 · JANUARY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Extended Survival and Prognostic Factors for Patients With *ALK*-Rearranged Non–Small-Cell Lung Cancer and Brain Metastasis

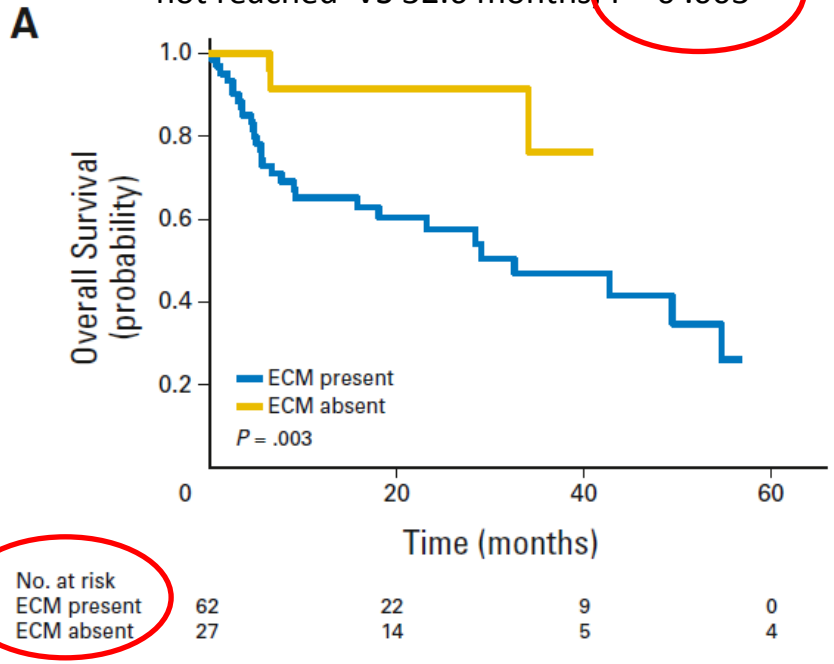
Kimberly L. Johung, Norman Yeh, Neil B. Desai, Terence M. Williams, Tim Lautenschlaeger, Nils D. Arvold, Matthew S. Ning, Albert Attia, Christine M. Lovly, Sarah Goldberg, Kathryn Beal, James B. Yu, Brian D. Kavanagh, Veronica L. Chiang, D. Ross Camidge, and Joseph N. Contessa

- 90 ALK-rearranged NSCLC patients with brain metastases
- 84 of 90 patients received radiotherapy to the brain (stereotactic radiosurgery [SRS] or whole-brain radiotherapy [WBRT])
- 86 of 90 received tyrosine kinase inhibitor (TKI) therapy

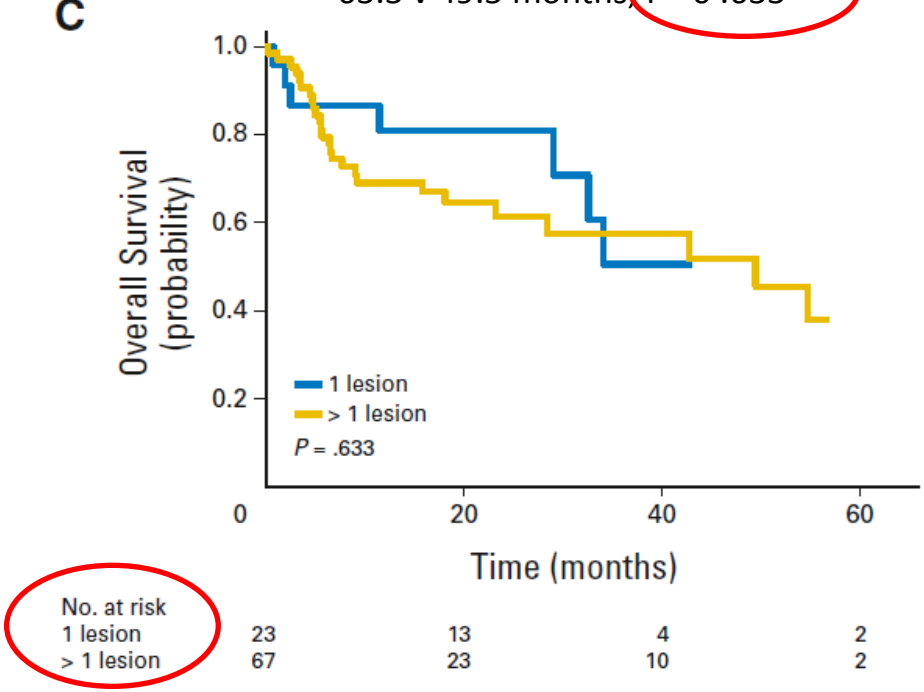
Kimberly L. ,et al. J ClinOncol 2015, 34:123-129

Results

not reached VS 32.6 months; P =0 .003



63.3 v 49.5 months; P =0 .633



OS was significantly longer for patients with metastatic disease **limited to the brain** compared with patients with **extracranial metastasis(ECM) and brain metastases**

There was no survival difference for patients presenting with a single brain metastasis versus . one more metastasis

Kimberly L. ,et al. J ClinOncol 2015, 34:123-129

VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Trial of Stereotactic Body Radiation Therapy Combined With Erlotinib for Patients With Limited but Progressive Metastatic Non–Small-Cell Lung Cancer

Puneeth Iyengar, Brian D. Kavanagh, Zabi Wardak, Irma Smith, Chul Ahn, David E. Gerber, Jonathan Dowell, Randall Hughes, Ramzi Abdulrahman, D. Ross Camidge, Laurie E. Gaspar, Robert C. Doebele, Paul A. Bunn, Hak Choy, and Robert Timmerman

- A single-arm phase II study
  - Biopsy proven stage IV NSCLC with up to six active extracranial lesions receive SBRT plus erlotinib at or beyond second-line therapy
- The primary object: 6-month PFS
- Erlotinib administration began 1 week before SBRT and continued during and after SBRT until disease progression or intolerable toxicity
- All patients had every site of disease treated with SBRT

PuneethIyengar , et al. J ClinOncol 2015, 32:3824-3830

Results

- 24 patients with stage IV NSCLC with six or fewer sites of disease were enrolled onto the study between 2007 and 2013
  - Mean follow-up -16.8 months (range, 3.4-60.3 months)

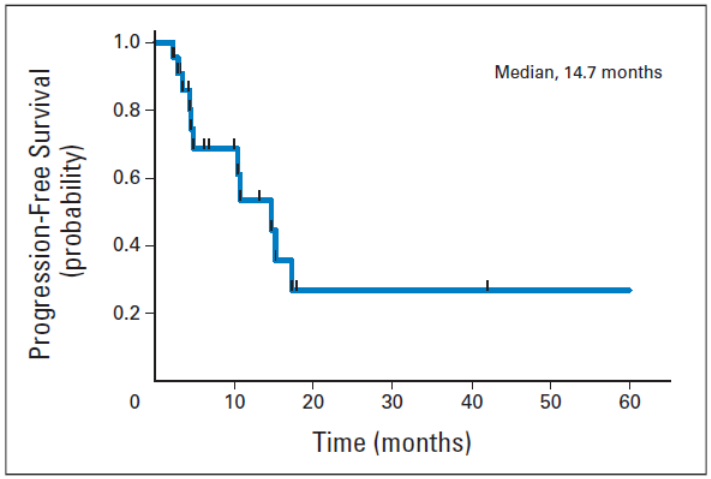


Fig 1. Kaplan-Meier analysis of progression-free survival (PFS) in months for all 24 patients enrolled on the study.

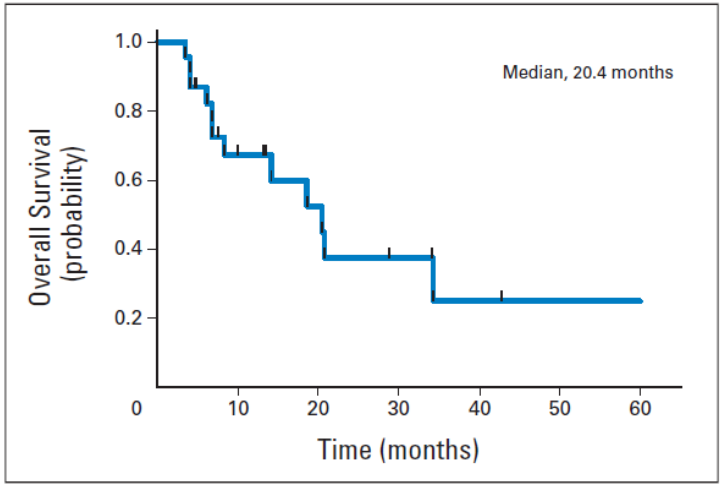


Fig 2. Kaplan-Meier analysis of overall survival (OS) in months for all 24 patients enrolled on the study.

median progression-free survival 14.7 months

median overall survival 20.4 months

PuneethIyengar , et al. J ClinOncol 2015, 32:3824-3830

VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY

E D I T O R I A L

accompanying editorial

Are We Expanding Oligometastatic Non–Small-Cell Lung Cancer Using Advanced Radiotherapeutic Modalities?

Salma K. Jabbour, *Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ*

See accompanying article on page 3824

- EGFR status was evaluated in 13 of 24 patient tumors with none harboring mutations
- Advent of targeted agents can allow for longer patient survivals and thereby improve the ability of local therapy

Iyengar et al[7] used systemic therapy that consisted of erlotinib beginning 1 week before SBRT and continuing during and after SBRT until disease progression or unacceptable toxicity. Because evaluation of epidermal growth factor receptor (*EGFR*) mutation status was not mandatory for this clinical trial, only 54% of patients had a mutational status determined, and none harbored an *EGFR* mutation. However, uncertainty exists about the impact of erlotinib on the survival of the remaining patients who did not undergo mutational status determination. Although it is unlikely that targeting the *EGFR* mutation influenced survival outcomes and that the main source of the survival benefit was SBRT, one cannot discern the relative benefits of SBRT and the possibility that an actionable EGFR mutation affected survival in some proportion of untested patients. The authors point out that there were no significant differences in survivals between the group

Jabbour SK . J Clin Oncol. 2014 1;32(34):3794-6.

Synchronous vs Metachronous Oligometastatic Disease

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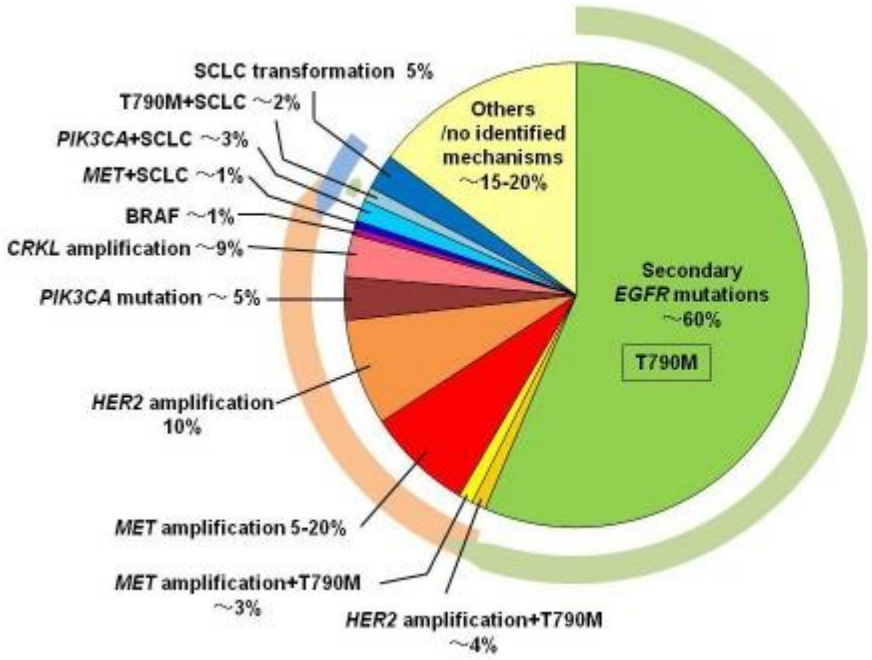
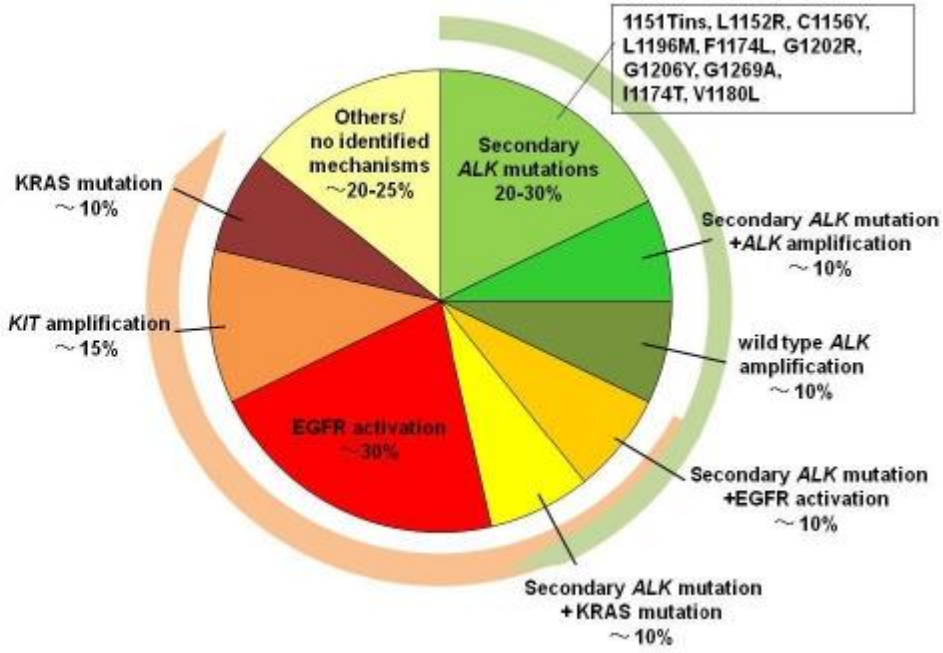
M. Reck, et al. Ann Oncol. 2014 Sep;25 Suppl 3:iii27-39

Molecular Mechanisms of Drug Resistance

- Most resistance mechanisms to kinase inhibitors result in pathway reactivation
- If reactivation is due to a mutation in the drug target then need:
  - Better drug
  - Combinations of drugs against the same target
- If reactivation is due to bypass mechanism need combination therapy

Mechanisms of drug resistance to EGFR and ALK targeted therapies





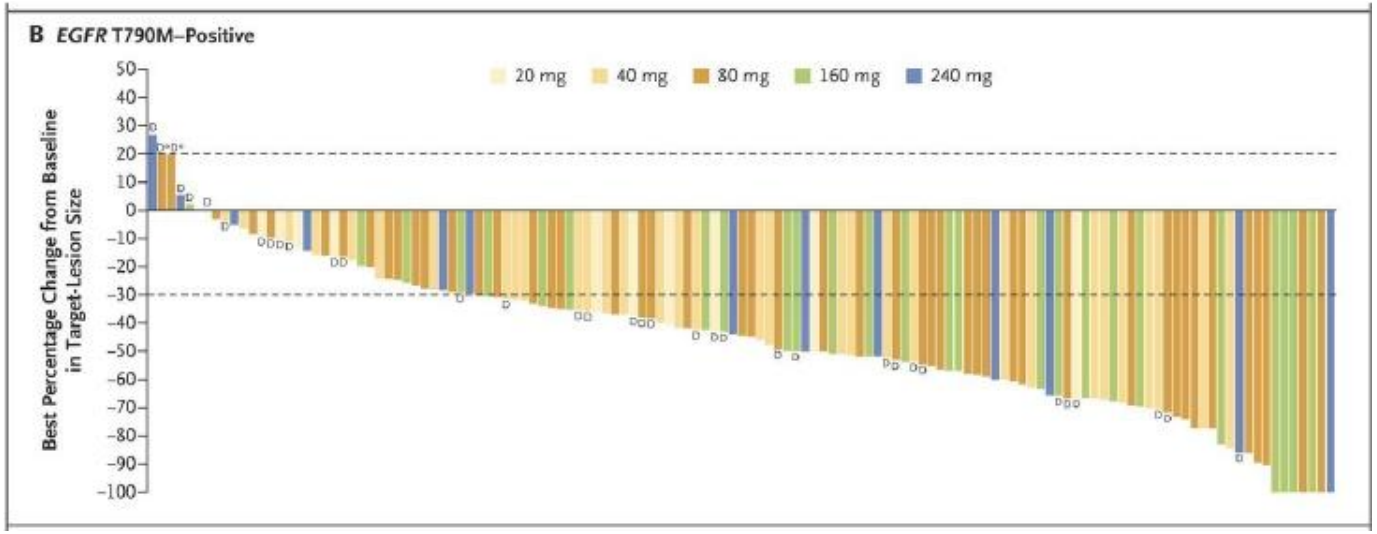
EGFR mutant

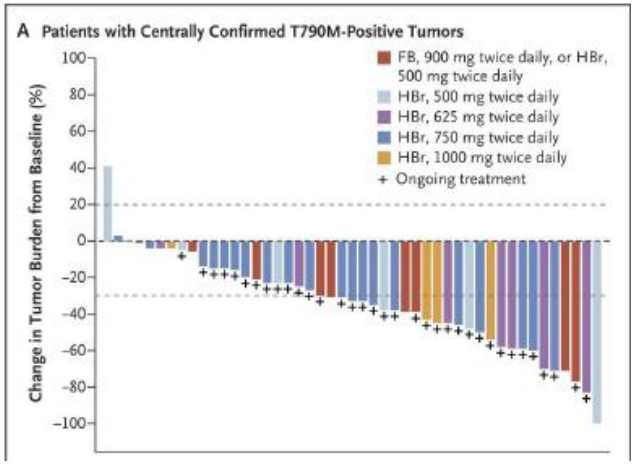
ALK rearranged

EGFR/ALK target alteration
Alternative pathway activation
Histologic transformation

Junko Tanizaki

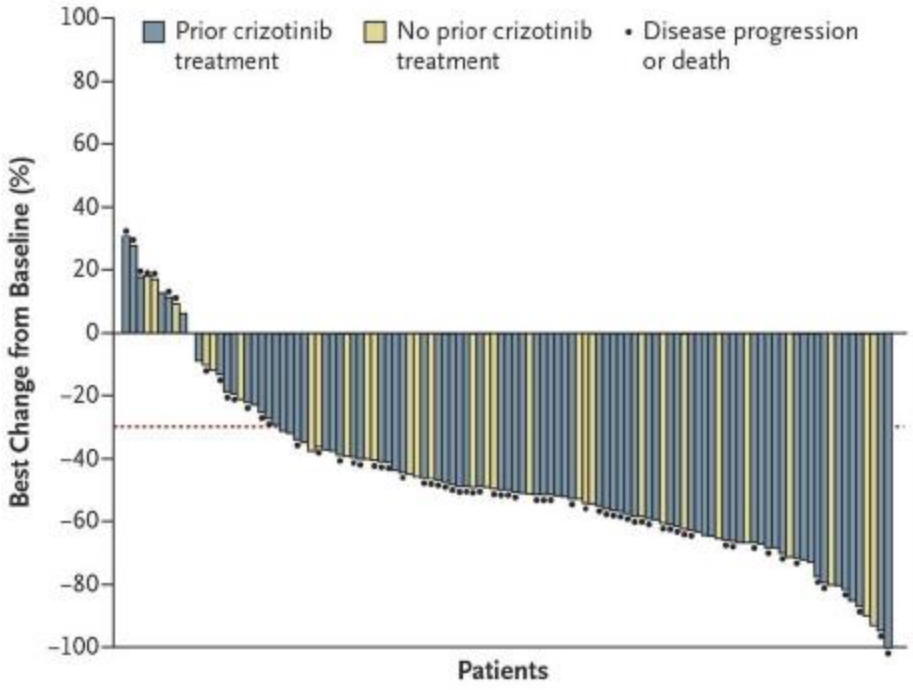
Efficacy of mutant selective EGFR inhibitors in EGFR inhibitor resistant EGFR T790M NSCLC

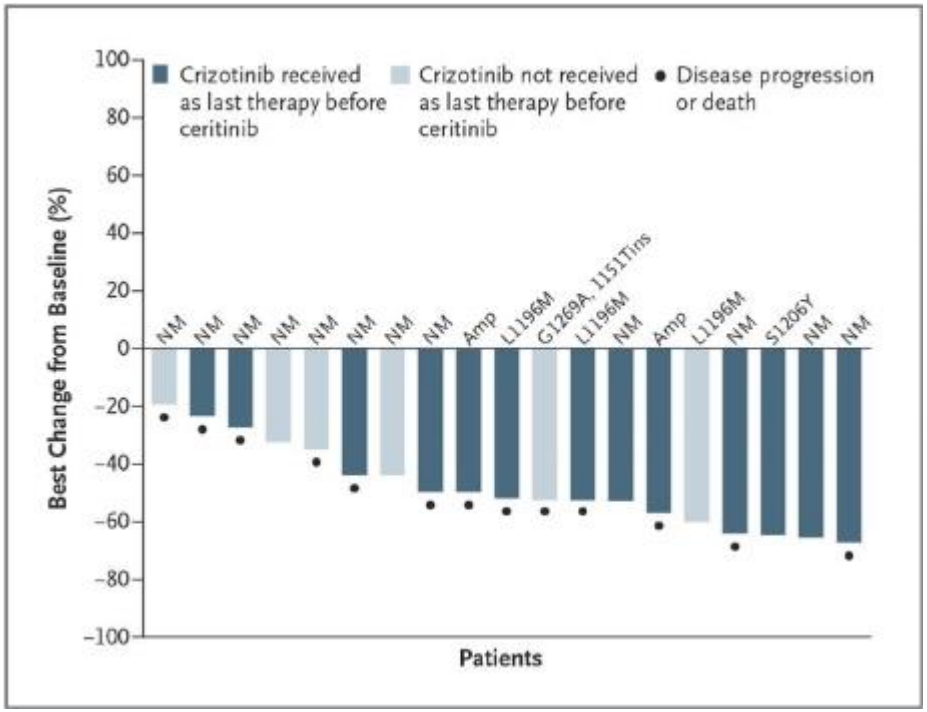




Jänne et al. NEJM 2015; Sequist et al. NEJM 2015

Ceritinib in ALK Rearranged NSCLC



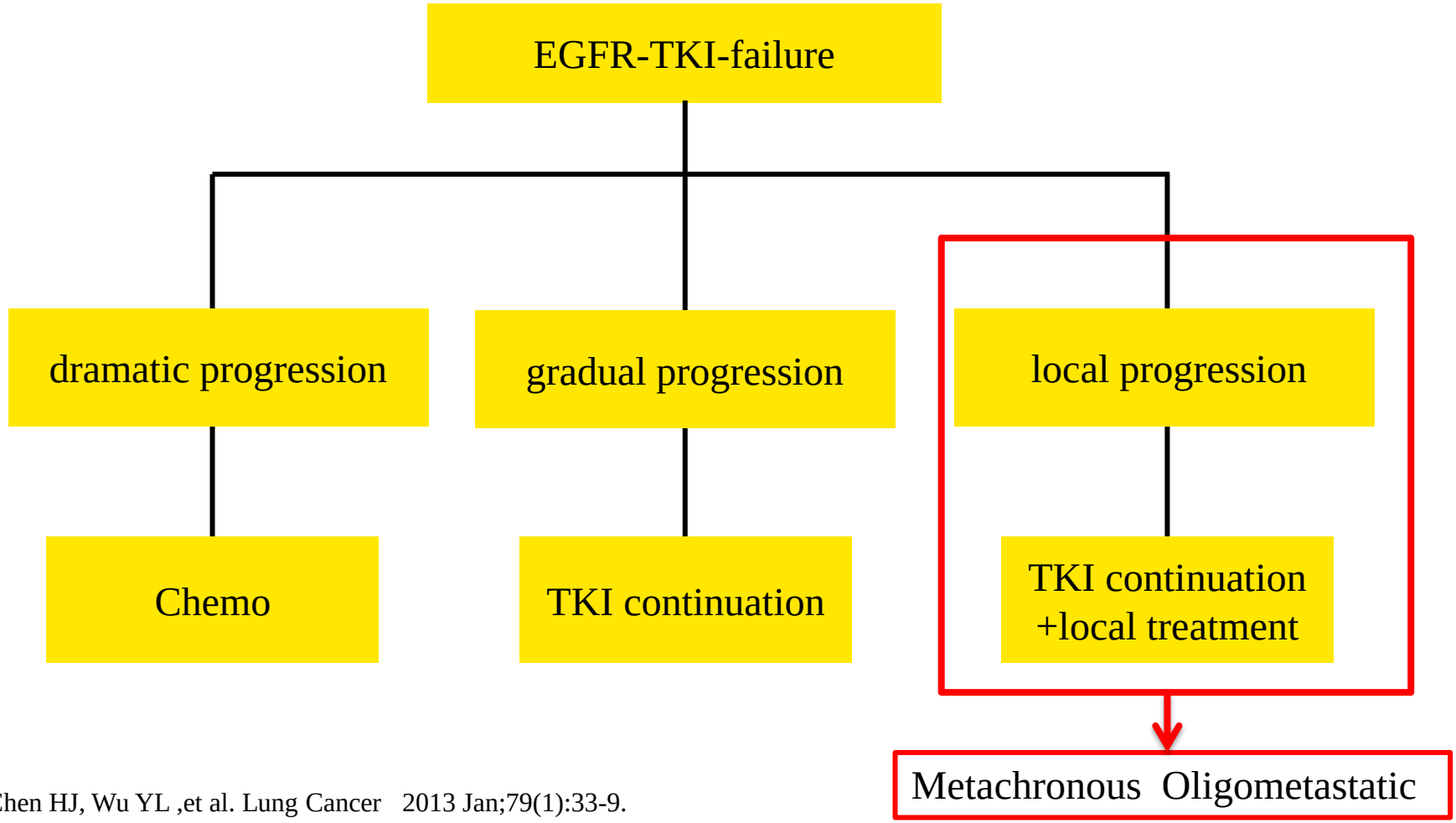


Overall response rate: 58% (95% confidence interval [CI], 48 to 67)

Patients with prior crizotinib
Response rate: 56% (95% CI, 45 to 67)

Shaw AT et al. N Engl J Med 2014;370:1189-1197.

Clinical modes of EGFR tyrosine kinase inhibitor failure



Yang JJ, Chen HJ, Wu YL ,et al. Lung Cancer 2013 Jan;79(1):33-9.

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**

- Patients with progression after initial treatment with either crizotinib or erlotinib were considered for LAT to the site(s) of progression and continuation of the same oral targeted therapy
  - With either non-leptomeningeal CNS progression and/or less than 4 sites of eCNS progression, adequate PS *and good* tolerance of their targeted therapy (*n = 25)*

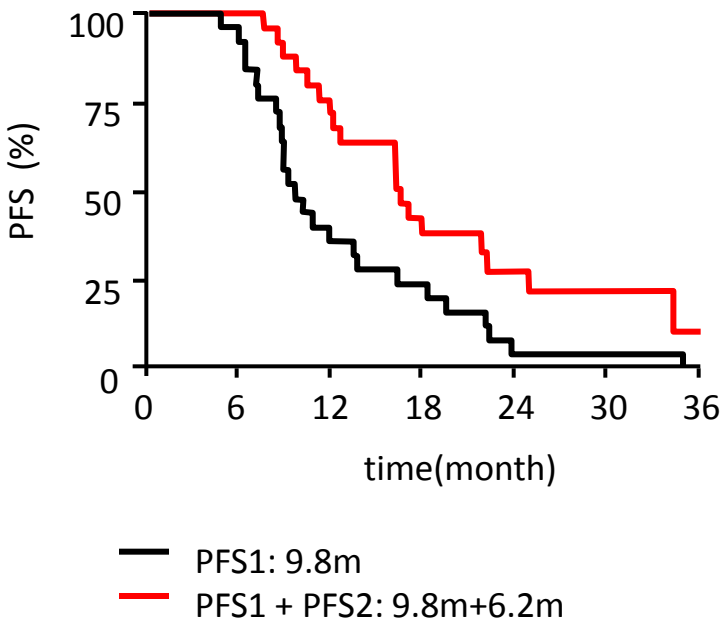
Weickhardt AJ, et al. J Thorac Oncol 2012; 7(12):1807-1814.

Local ablative therapy combined with TKI

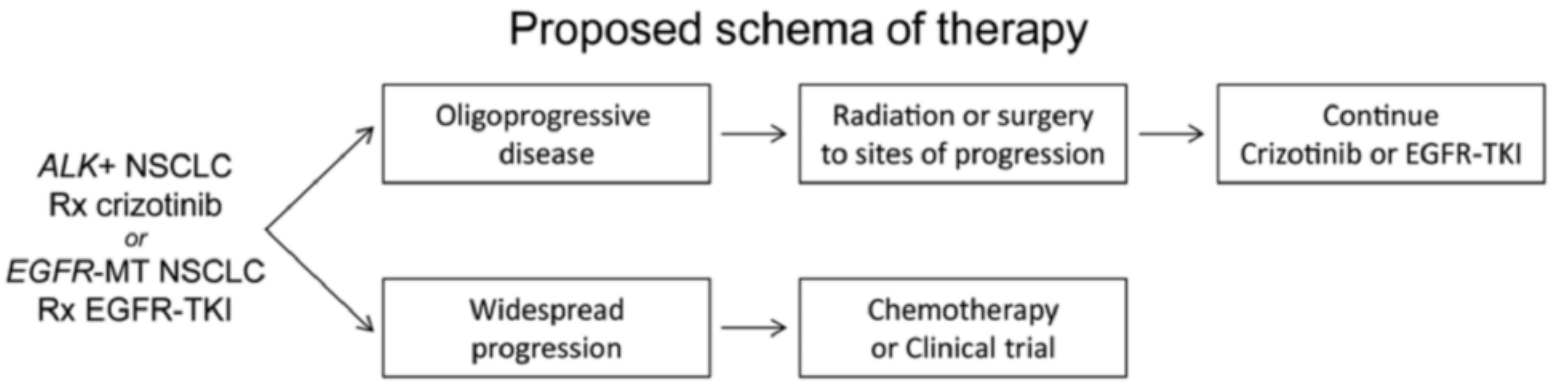
- 65 patients with oncogene-driven NSCLC patients(EGFR m+ or ALK+) ,treated with tyrosine kinase inhibitors experience
- PFS 1: Initial response to the respective kinase inhibitors, and <4site of first progression,received either radiation or surgery
- PFS 2: The subsequent median progression-free survival from the time of first progression

  - Result
    - 38ALK+patients，28PD(74%)
      - Median PFS1 = 9.0month
    - EGFR-MT NSCLC treated with erlotinib，23PD(85%)
      - Median PFS1 = 13.8month
    - All patients PFS1 = 10.3month
  - 25 of 51 patients (49%) who progressed were deemed suitable for local therapy

Site of First Progression	N	PFS1 (95% CI)	PFS2 (95% CI)
CNSand/ Or eCNS	25	9.8month 8.8 – 13.8	6.2month 3.7 – 8.0



Weickhardt AJ, et al. J Thorac Oncol 2012; 7(12):1807-1814.



- Proposed schema for incorporating local ablative therapy into therapy at time of first progression with ALK+ or EGFR-MT NSCLC patients treated with TKI therapy

Weickhardt AJ, et al. J Thorac Oncol 2012; 7(12):1807-1814.

ORIGINAL ARTICLE

Local Therapy with Continued EGFR Tyrosine Kinase Inhibitor Therapy as a Treatment Strategy in *EGFR*-Mutant Advanced Lung Cancers That Have Developed Acquired Resistance to EGFR Tyrosine Kinase Inhibitors

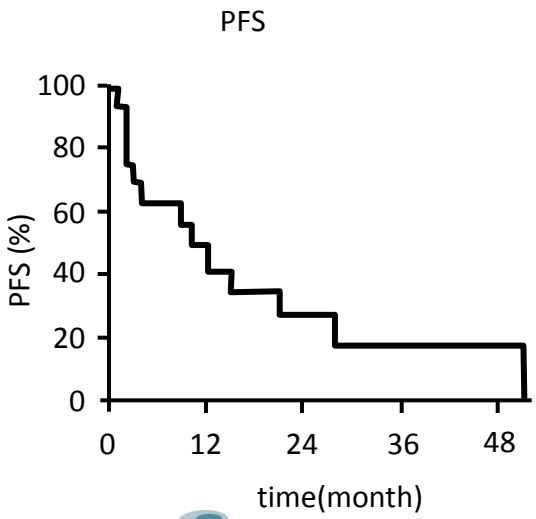
Helena A. Yu, MD, Camelia S. Sima, MD, MS,‡ James Huang, MD,† Stephen B. Solomon, MD,§ Andreas Rimner, MD,‖ Paul Paik, MD,* M. Catherine Pietanza, MD,* Christopher G. Azzoli, MD,* Naiyer A. Rizvi, MD,* Lee M. Krug, MD,* Vincent A. Miller, MD,* Mark G. Kris, MD,* Gregory J. Riely, MD, PhD**

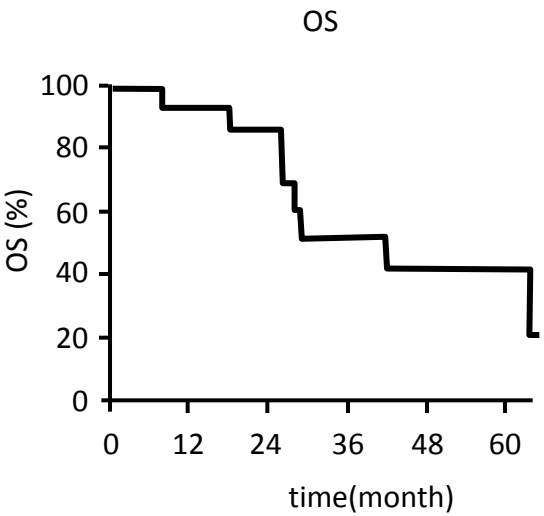
- Eighteen patients were identified, who received elective local therapy (surgical resection, radiofrequency ablation, or radiation)
- Local therapy was well tolerated, with 85% of patients restarting TKI therapy within 1 month of local therapy
- All patients except one had oligometastatic disease (<5 sites of disease) at the time of local therapy

Yu HA, et al. J ThoracOncol. 2013;8: 346–351.

Local Therapy with Continued EGFR Tyrosine Kinase Inhibitor Therapy as a Treatment Strategy in *EGFR*-Mutant Advanced Lung Cancers That Have Developed Acquired Resistance to EGFR Tyrosine Kinase Inhibitors

- **184 pts with acquired resistance , 18 pts received local therapy**
  - **excluding** CNS PD
- Since local treatment
  - Median TTP : 10 month
  - **median time from local therapy until change in systemic therapy** : 22 month
  - Median OS : 41 month



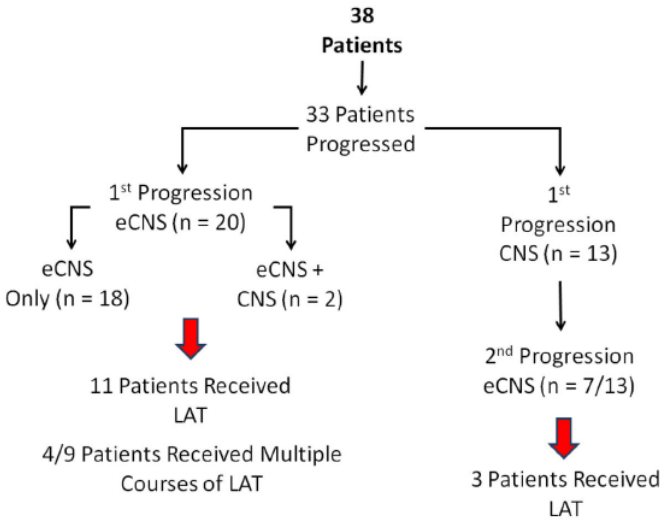


Local therapy	N=18
Lung	**15**
radio frequence(RFA)	**2**
radiotherapy	**2**
Lobectomy	**7**
Wedge resection	**1**
Pneumonectomy	**3**
LN radiotherapy(Mediastinal / supraclavicular)	**1**
Adrenalectomy	**2**

Yu HA, et al. J ThoracOncol. 2013;8: 346–351.

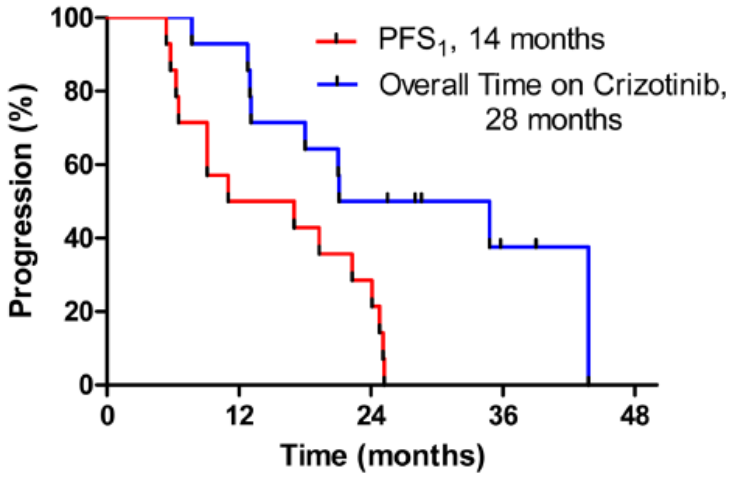
Stereotactic Radiation Therapy can Safely and Durably Control Sites of Extra-Central Nervous System Oligoprogressive Disease in ALK-Positive Lung Cancer Patients Receiving Crizotinib

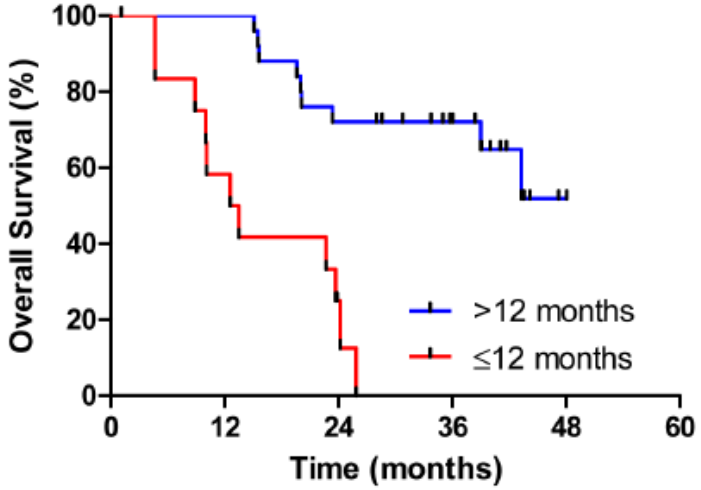
- 33 of 38 patients progressed on crizotinib
- 14 had eCNS progression received 1–3 courses of LAT with radiotherapy
- Crizotinib was continued until eCNS progression was beyond Oligoprogressive criteria or otherwise not suitable for further LAT



Gregory N. et al. Int J RadiatOncolBiol Phys. 2014 15; 88(4): 892–898

Results





Median overall time on crizotinib among those treated with LAT versus those who progressed but were not suitable for LAT was 28 and 10.1 months, respectively.

Patients remaining on crizotinib for >12 months vs ≤12 months had a 2 year OS of 72% vs 12%, respectively ($p < 0.0001$).

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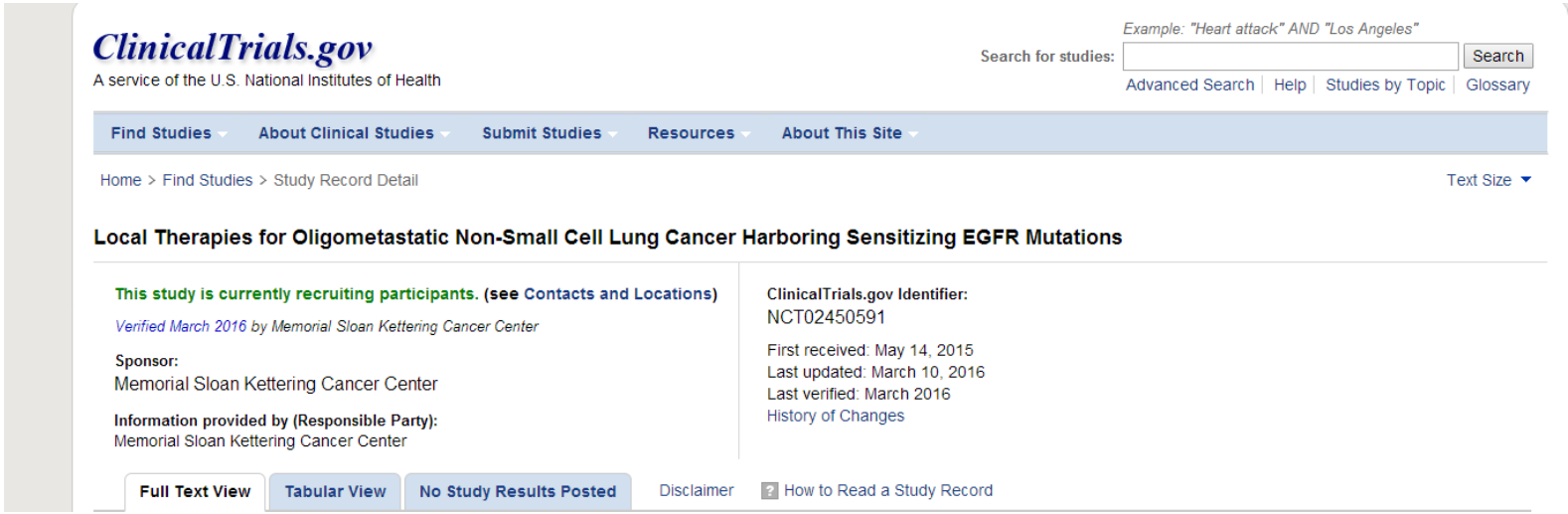
Future



•Oligometastatic NSCLC patients will undergo induction erlotinib for 12 weeks.

•At the conclusion of 12 weeks on TKI , patients without disease progression will undergo definitive local treatment to all remaining sites of disease.

• After local therapy, erlotinib will be resumed until progression of disease by RECIST criteria.

•Endpoint Classification: Safety/Efficacy Study

Summary

- In theory, " Oligometastatic " is advanced disease, the treatment aims to prolong life as much as possible while maximizing the quality of life
- Many studies have shown primary tumors and metastases biological behavior is not consistent, the systemic treatment combined with local treatment will benefit the " Oligometastatic " NSCLC patients
- Randomized clinical trials will be necessary to prospectively evaluate the effect of aggressive local therapy plus target therapy

Thank you