Memorial Sloan Kettering Cancer Center

Optimal Management of Oligometastatic Disease

Mark G Kris, MD
Memorial Sloan Kettering Cancer Center
New York, New York USA

Management of Oligometastases in Lung Cancers

Patient

- 68 y/o woman, a never smoker
- Stage IV *EGFR*-mutant lung cancer (L858R) with metastases to ischium and brain
- Treated with erlotinib 75 mg and bevacizumab –PR. Brain lesion resolves
- Month 13, after 10 bevacizumab and erlotinib X 13 mo, Residual 2.7 cm lesion resected. R0. T790M present.
- Month 19, after 16 bevacizumab and erlotinib X 19 mo, 3 fx IGRT to ischium
- Month 24, bevacizumab stopped after 23 doses due to intolerance of antihypertensive meds
- Month 26, remains NED

Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Optimal Management of Oligometastatic Disease

Mark G Kris, MD
Memorial Sloan Kettering Cancer Center
New York, New York USA

Management of Oligometastases in Lung Cancers

Disclosures

Consultant:
Astrazeneca
Genentech/Roche

Additional Disclosures

I was born a medical oncologist but was raised by thoracic surgeons

I am a chemotherapy guy who has gone molecular

Management of Oligometastases in Lung Cancers

Definitions

- Local Therapy for:
  - Oligometastases
  - Residual Disease after Systemic Therapy
  - Isolated (Symptomatic) Sites of Relapse

Oligometastases
A decades-old concept

EDITORIAL

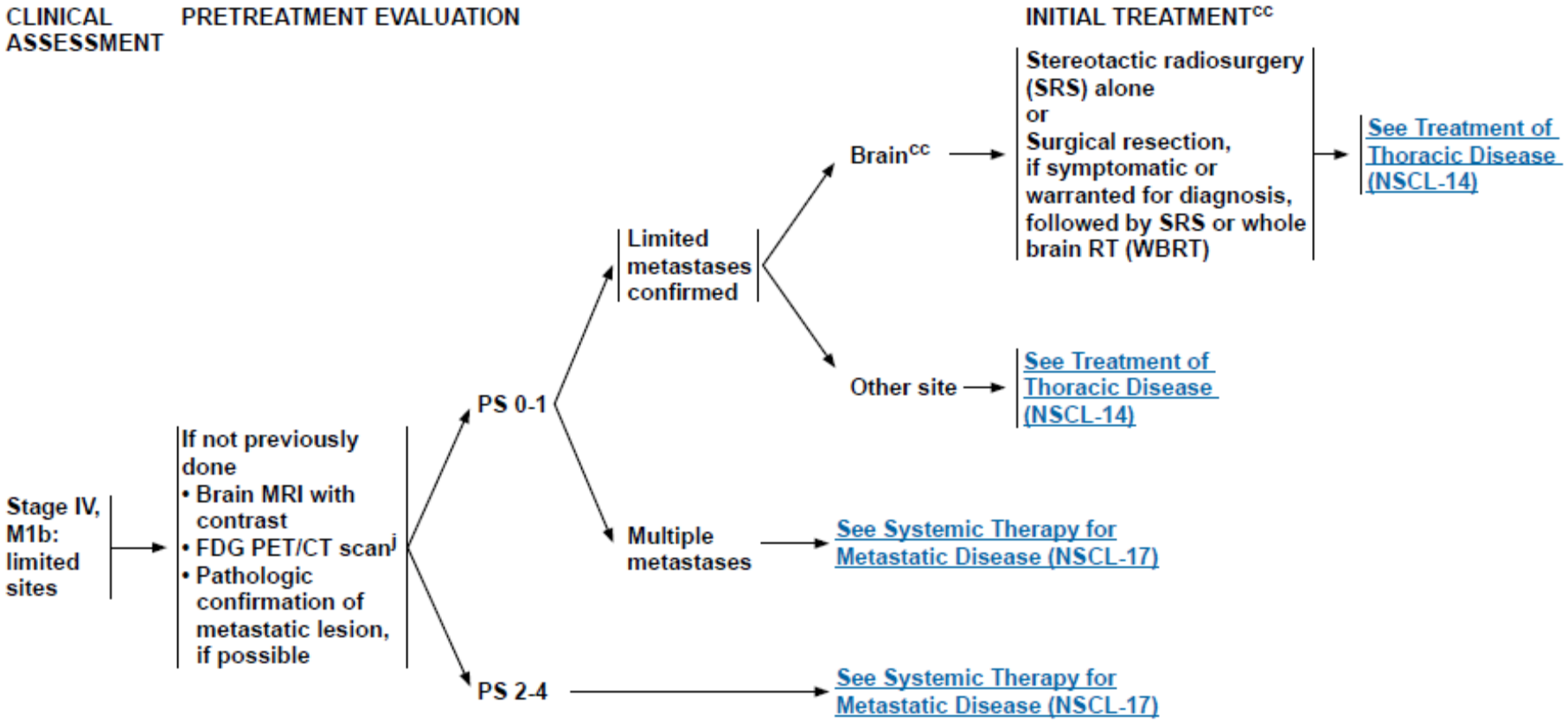
Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] 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.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] 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

Journal of Clinical Oncology, Vol 13, No 1 (January), 1995: pp 8-10

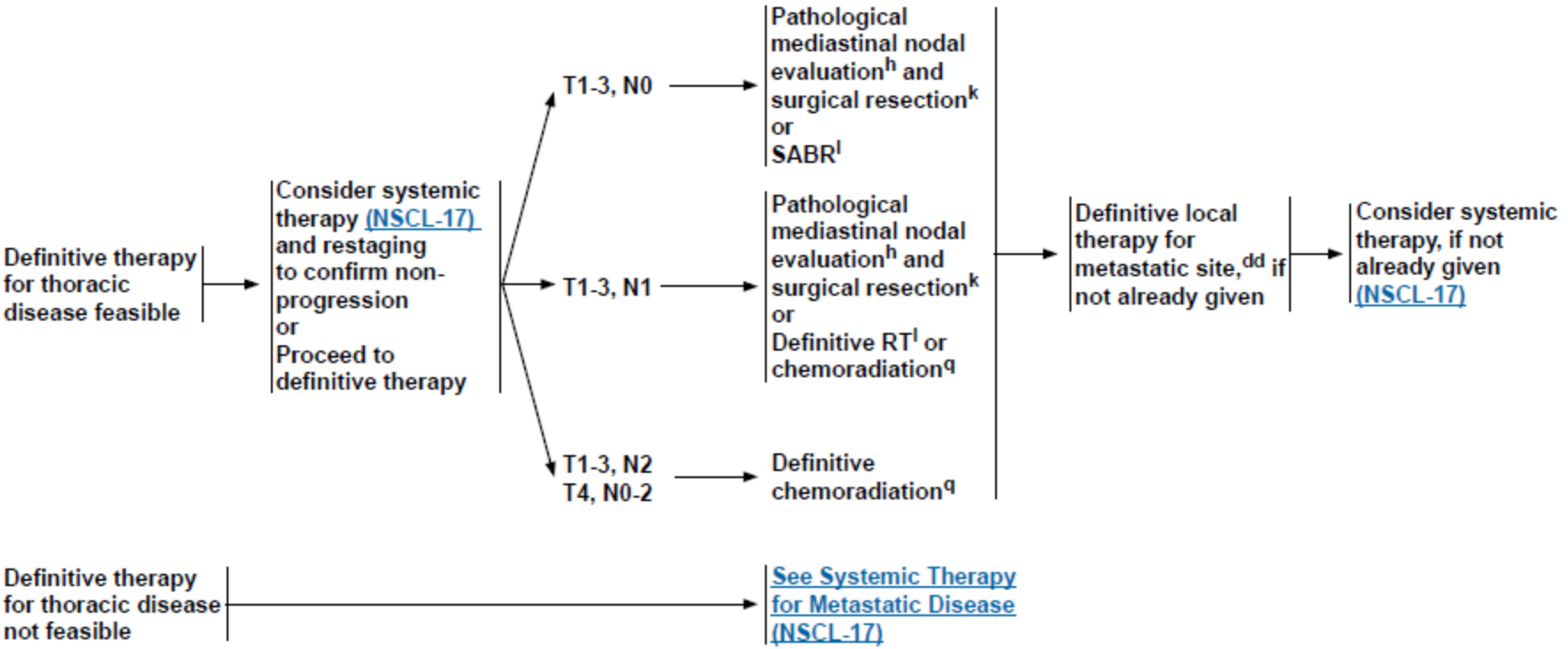
Samuel Hellman
Ralph R. Weichselbaum
The University of Chicago
Chicago, IL



[j]PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation.
[cc]See NCCN Guidelines for Central Nervous System Cancers.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT OF THORACIC DISEASE



[h]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[k]See Principles of Surgical Therapy (NSCL-B).
[l]See Principles of Radiation Therapy (NSCL-C).
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[dd]Typically, RT (including SABR) or surgical resection.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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**

Introduction: Many patients with oncogene-driven non–small-cell lung cancer (NSCLC) treated with tyrosine kinase inhibitors experience limited sites of disease progression. This study investigated retrospectively the benefits of local ablative therapy (LAT) to central nervous system (CNS) and/or limited systemic disease progression and continuation of crizotinib or erlotinib in patients with metastatic *ALK* gene rearrangement (*ALK*+) or *EGFR*-mutant (*EGFR*-MT) NSCLC, respectively.

Methods: Patients with metastatic *ALK*+ NSCLC treated with crizo-

targeted agent, and is associated with more than 6 months of additional disease control.

Key Words: *EGFR*-mutant non–small-cell lung cancer, anaplastic lymphoma kinase gene arrangement non–small-cell lung cancer, Radiation therapy, Oligoprogressive disease.

(*J Thorac Oncol.* 2012;7: 1807–1814)

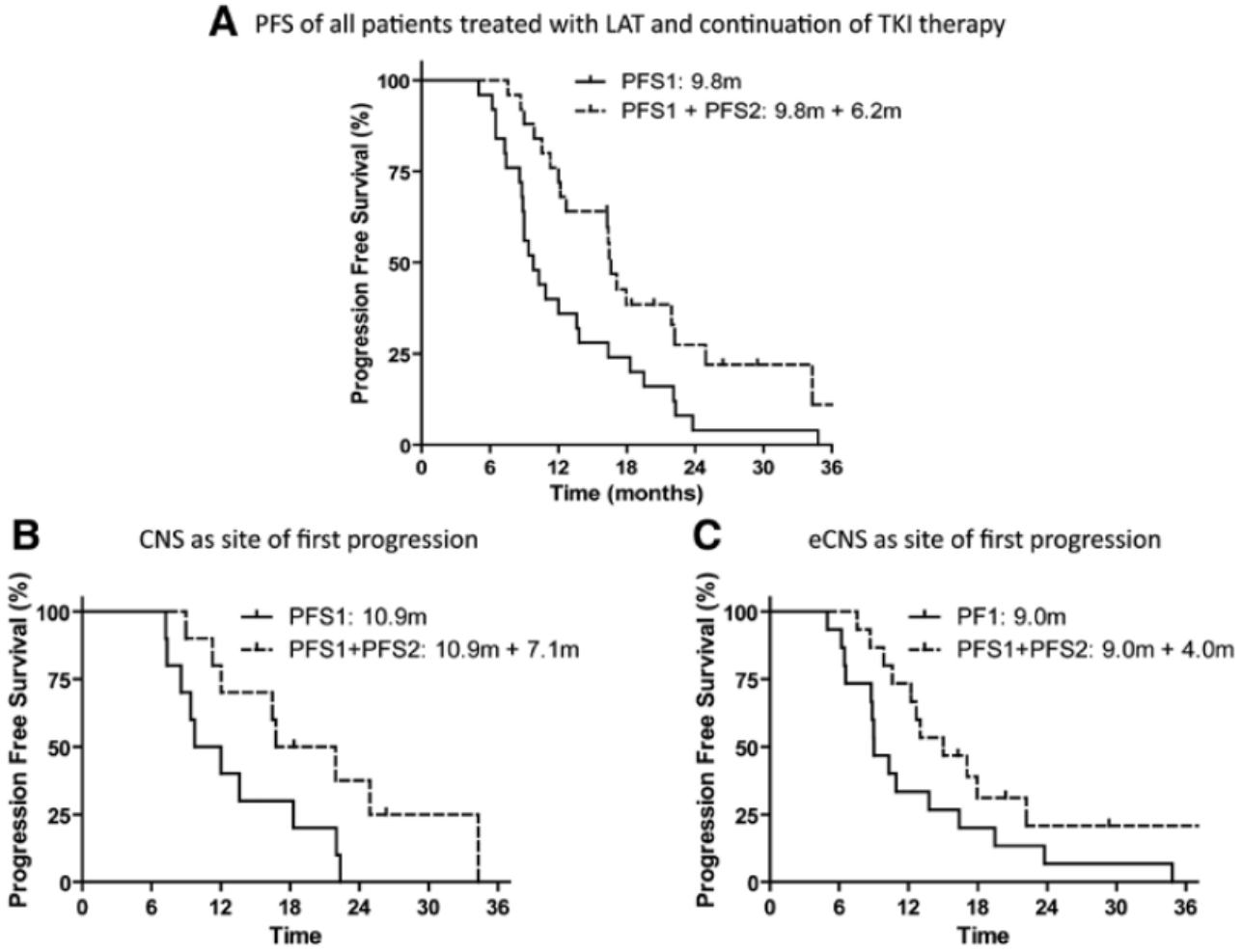


FIGURE 1. *A*, PFS1 and PFS1+PFS2 survival curves of all 25 patients treated with LAT. *B*, Ten patients treated with LAT who first progressed only in the CNS. *C*, Fifteen patients treated with LAT who first progressed in extra-CNS locations, including three patients with simultaneous CNS and eCNS progression. PFS1, median progression-free survival; PFS2, progression-free survival from the time of first progression; LAT, local ablative therapy; CNS, central nervous system; eCNS, extra-CNS.

Weickhardt et al. J Thorac Oncol 2012

Memorial Sloan Kettering Cancer Center

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**

Background: Development of acquired resistance limits the utility of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) for the treatment of *EGFR*-mutant lung cancers. There are no accepted targeted therapies for use after acquired resistance develops. Metastasectomy is used in other cancers to manage oligometastatic disease. We hypothesized that local therapy is associated with improved outcomes in patients with *EGFR*-mutant lung cancers with acquired resistance to EGFR TKI.

Methods: Patients who received non–central nervous system local therapy were identified by a review of data from a prospective biopsy protocol for patients with *EGFR*-mutant lung cancers with acquired resistance to EGFR TKI therapy and other institutional biospecimen registry protocols.

Results: 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. The median time to progression after local therapy was 10 months (95% confidence interval [CI]: 2–27 months). The median time until a subsequent change in systemic therapy was 22 months (95% CI: 6–30 months). The median overall survival from local therapy was 41 months (95% CI: 26–not reached).

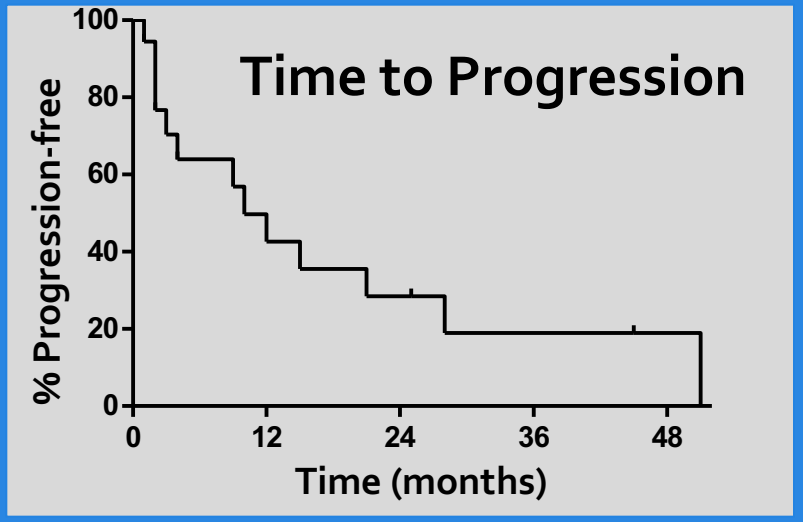
Conclusions: *EGFR*-mutant lung cancers with acquired resistance to EGFR TKI therapy are amenable to local therapy to treat oligometastatic disease when used in conjunction with continued EGFR inhibition. Local therapy followed by continued treatment with an EGFR TKI is well tolerated and associated with long PFS and OS. Further study in selected individuals in the context of other systemic options is required.

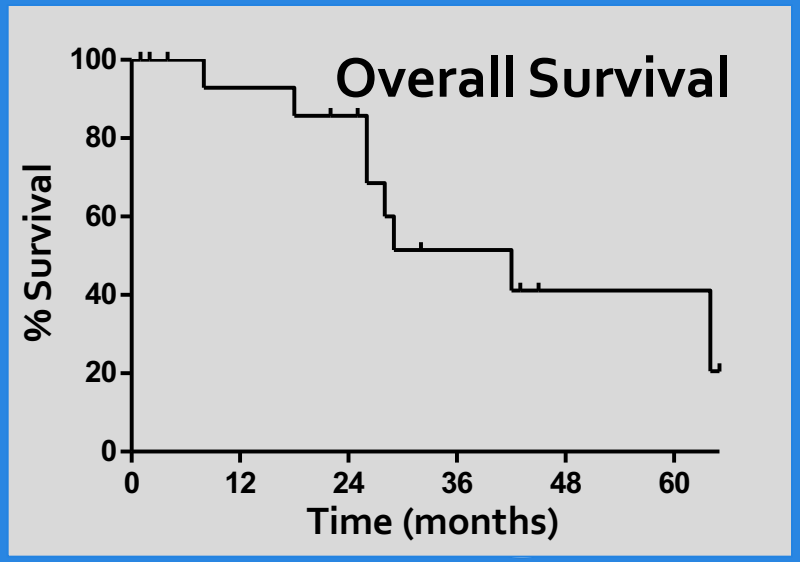
Key Words: EGFR-mutant lung cancer, Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors, Metastasectomy, Local therapy.

(*J Thorac Oncol.* 2013;8: 346–351)

Local Therapy for Oligo-Progression Outcomes

- The median time to progression after local therapy was **10 months** (95% CI: 2-27).
- The median time from local therapy until a change in systemic therapy was **22 months** (95%CI: 6 - 30).
- The median overall survival from local therapy was **41 months** (95% CI: 26-not reached).

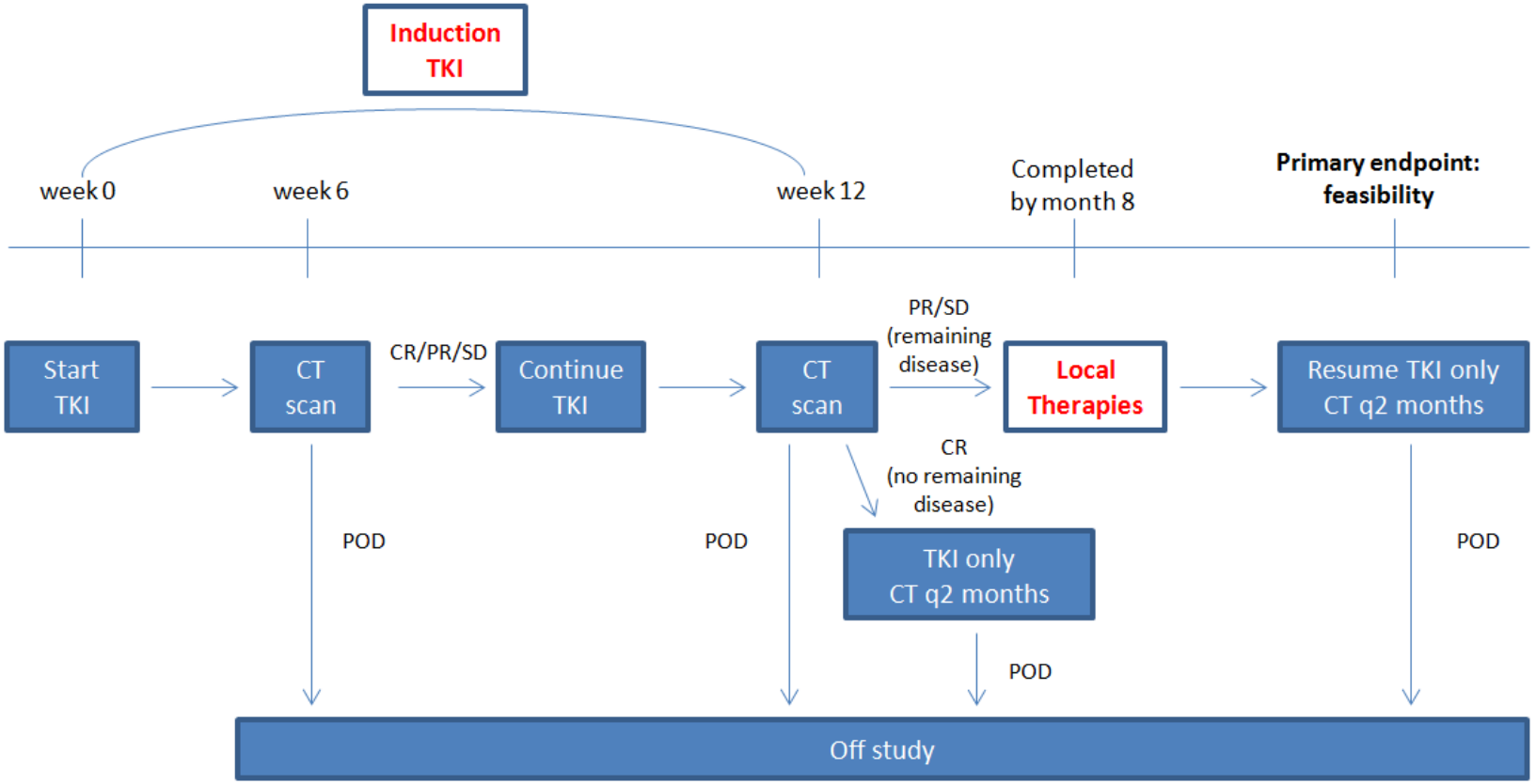




Yu et al. J Thorac Oncol 2013

IRB: 15-067 – Helena Yu, PI
Pilot Study of Local Therapies for Oligometastatic Lung Cancers Harboring Sensitizing *EGFR* Mutations

Patients with newly diagnosed lung cancers with a sensitizing *EGFR* mutation with ≤ 5 discrete metastatic deposits all amenable to definitive treatment with a local therapy (surgery, RT, or ablation)



Local consolidative therapy vs. maintenance therapy or observation for patients with 3 or fewer metastases from lung cancers without progression after initial systemic therapy

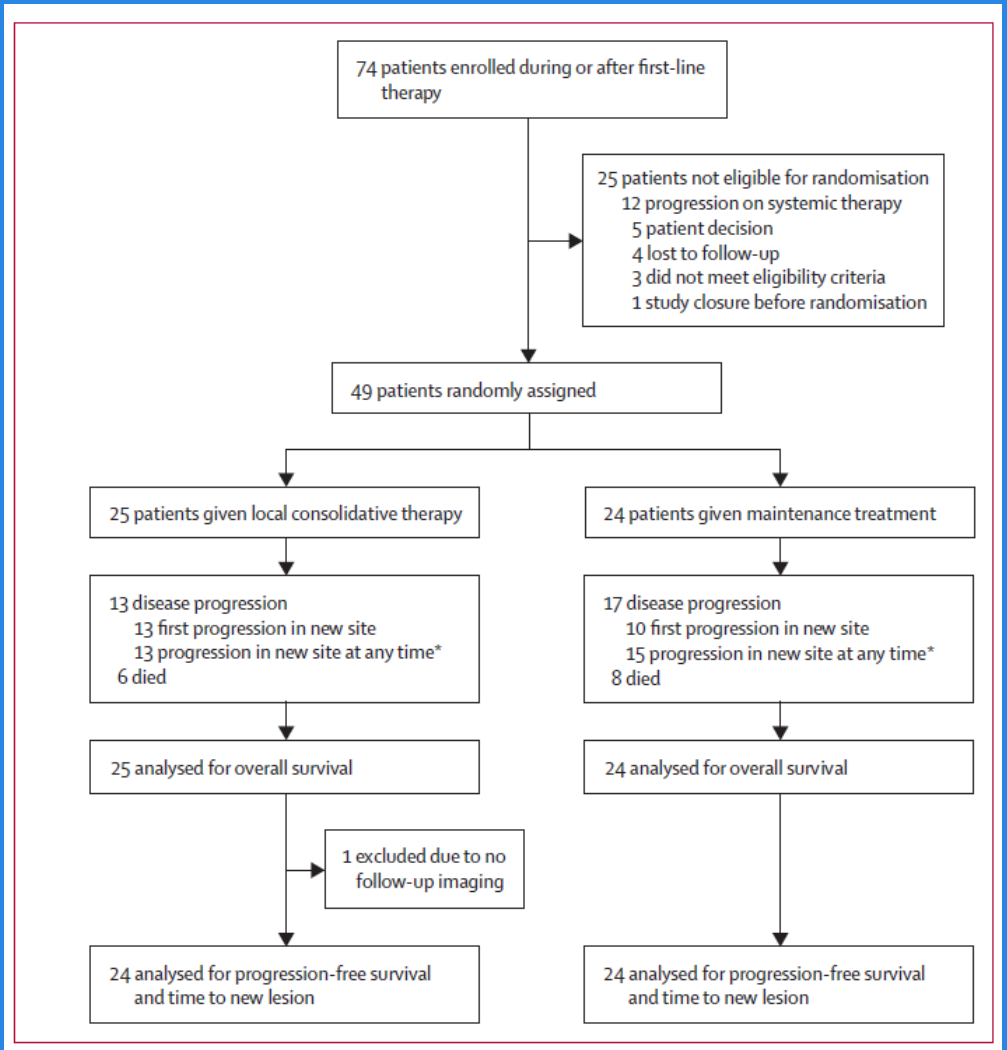


Figure 1: **Trial profile**
*Includes patients who developed a new lesion after their first progression event.

Gomez et al. Lancet Oncol 2016;17(12):1672-82.

Memorial Sloan Kettering Cancer Center

Oligometastatic Lung Cancers after Initial Chemotherapy And Local Consolidative Therapy or Maintenance

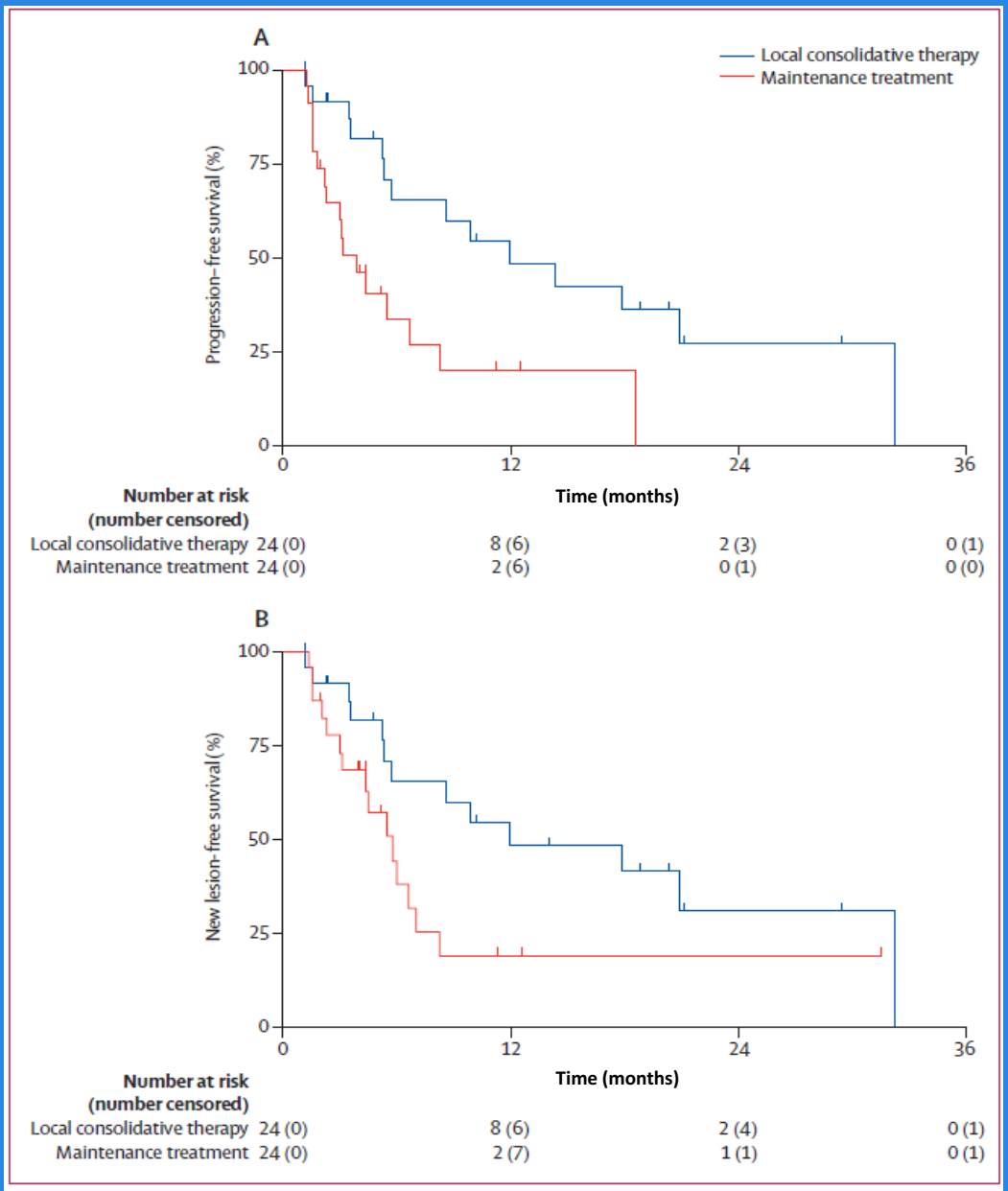


Figure 2: **Progression-free survival (A) and time to appearance of disease at a new site (B)**

Gomez et al. Lancet Oncol 2016

Management of Oligometastases in Lung Cancers

Conclusions

- Local therapies are appropriate in selected patients with metastatic lung cancers:
  - Oligometastases
  - Residual metastatic deposits after chemotherapy response
  - Single sites of progressive disease
- In general….consider local therapies only when systemic control is evident or a sure thing. Some exceptions: isolated brain and adrenal metastases, especially with no evidence of local nodal spread and resectable primary lesions
- Consider multimodality care for all persons with lung cancers