Memorial Sloan Kettering Cancer Center™

Local Therapies in Oncogene-Driven Lung Cancers

The Management of Oligo-Progression Disease

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Memorial Sloan Kettering Cancer Center

Management of Oligo-Progression in Patients with Oncogene-Driven Lung Cancers

Disclosures

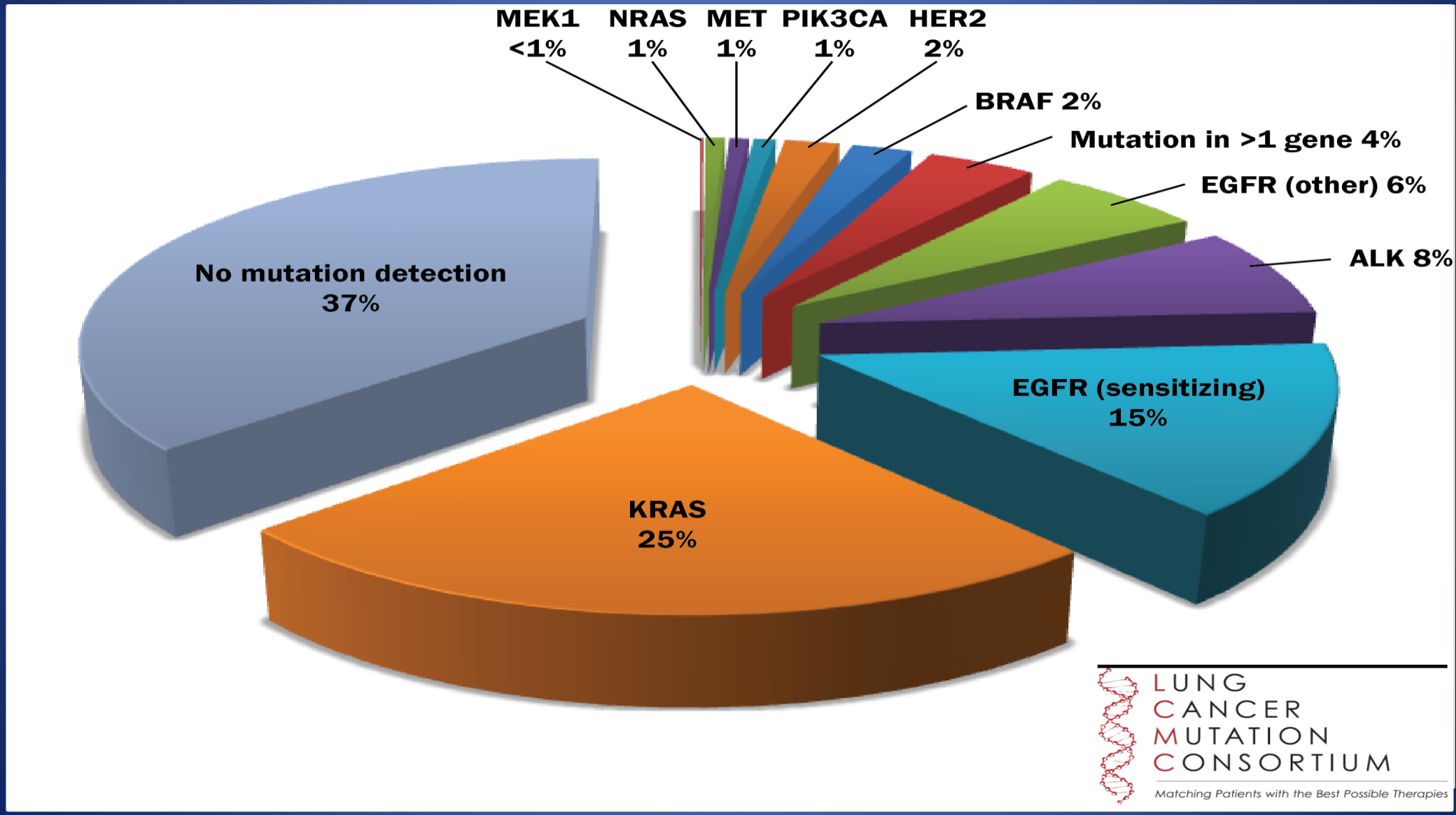
Consultant/Trial Support

Pfizer, Genentech/Roche, Novartis, PUMA, Clovis, Ariad, AstraZeneca, Daiichi Sankyo, Exelixis

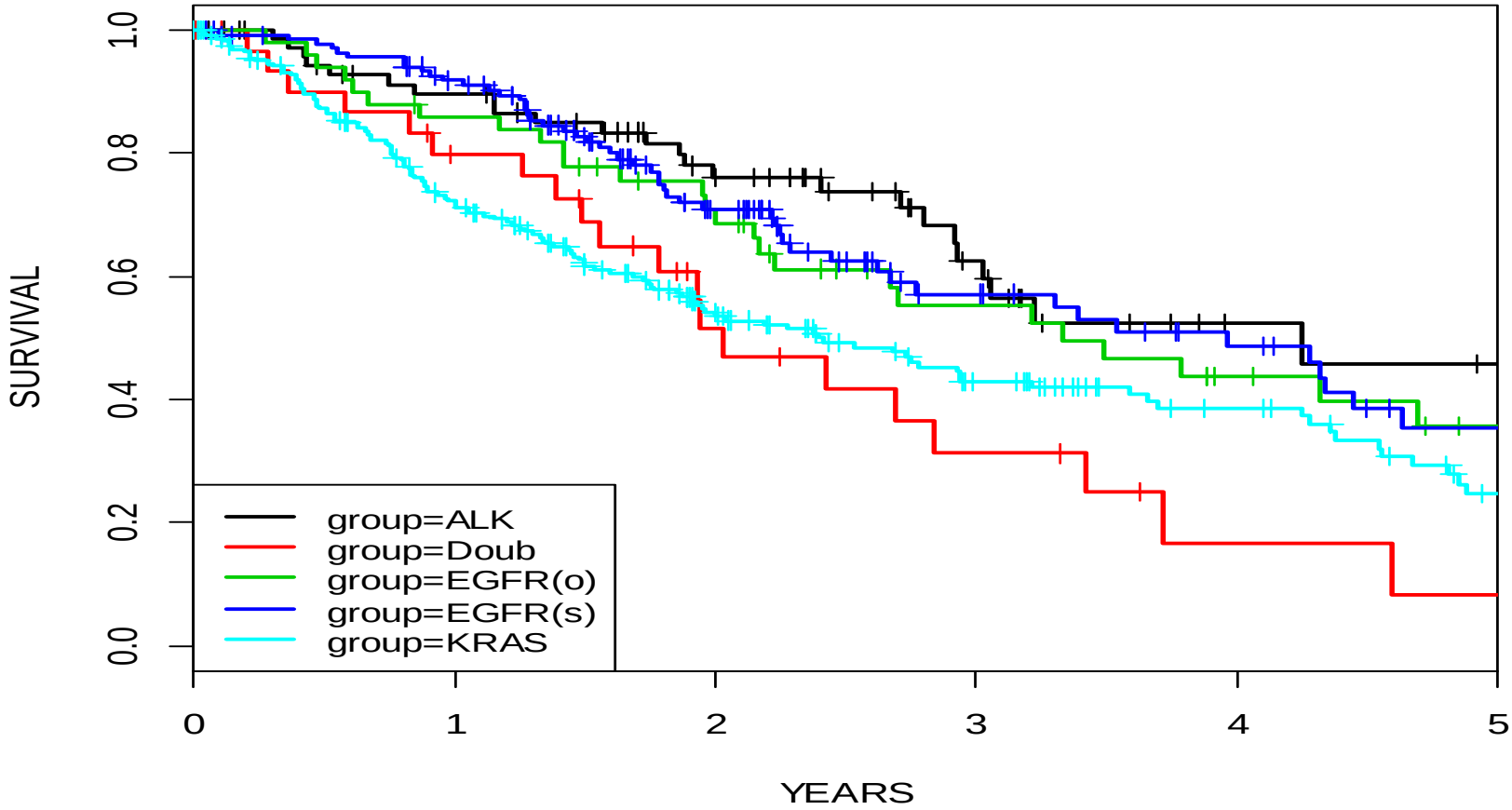
Employment/Ownership

None

LCMC: Frequency of Oncogenic Drivers
733 Specimens with All 10 Drivers Assayed



Survival with the five most frequent oncogenic drivers



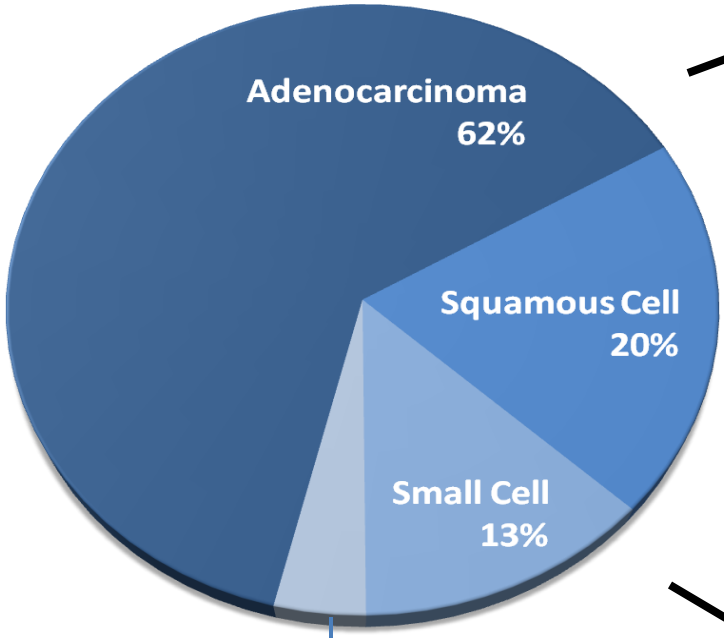
EGFR (sensitizing)	140	4.0 (2.67-5.37)
EGFR (other)	50	3.3 (2.22-6.20)
ALK	73	4.3 (3.02-NA)
KRAS	231	2.4 (1.91-3.58)
Doubletons	32	2.0 (1.55-4.59)

p=0.001

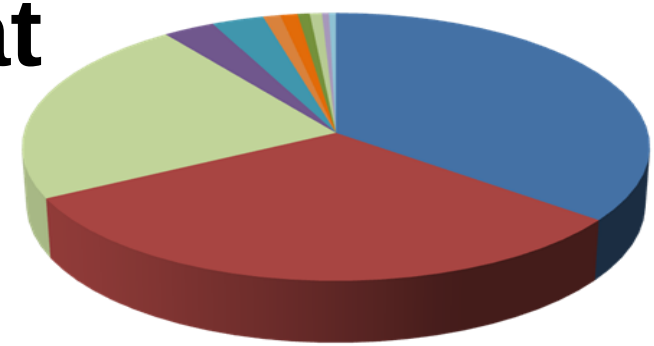
LUNG CANCER MUTATION CONSORTIUM

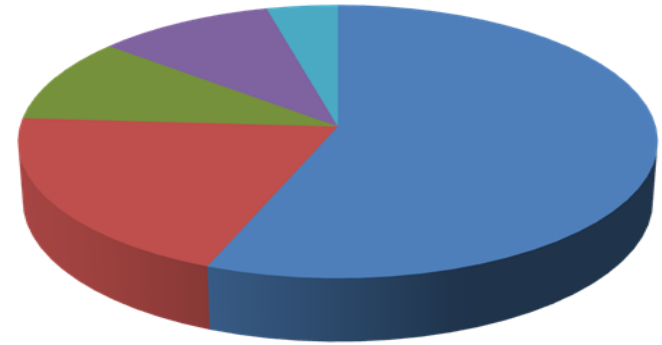
Matching Patients with the Best Possible Therapies

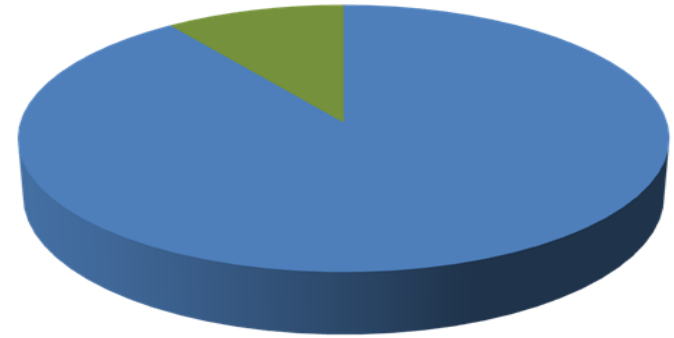
Using Driver Mutations to Classify and Treat All Lung Cancers



Carcinoid
Large Cell
Large Cell Neuroendocrine
5%







DRIVER MUTATIONS

Unknown	36%
KRAS	32%
EGFR	23%
ALK	3%
HER2	3%
Double Mt	1%
BRAF	<1%
PIK3CA	<1%
MET	<1%
MEK	<1%
NRAS	<1%

Unknown	56%
FGFR1 Amp	20%
PIK3CA	10%
PTEN	10%
DDR2	4%

Unknown	90%
PIK3CA	10%

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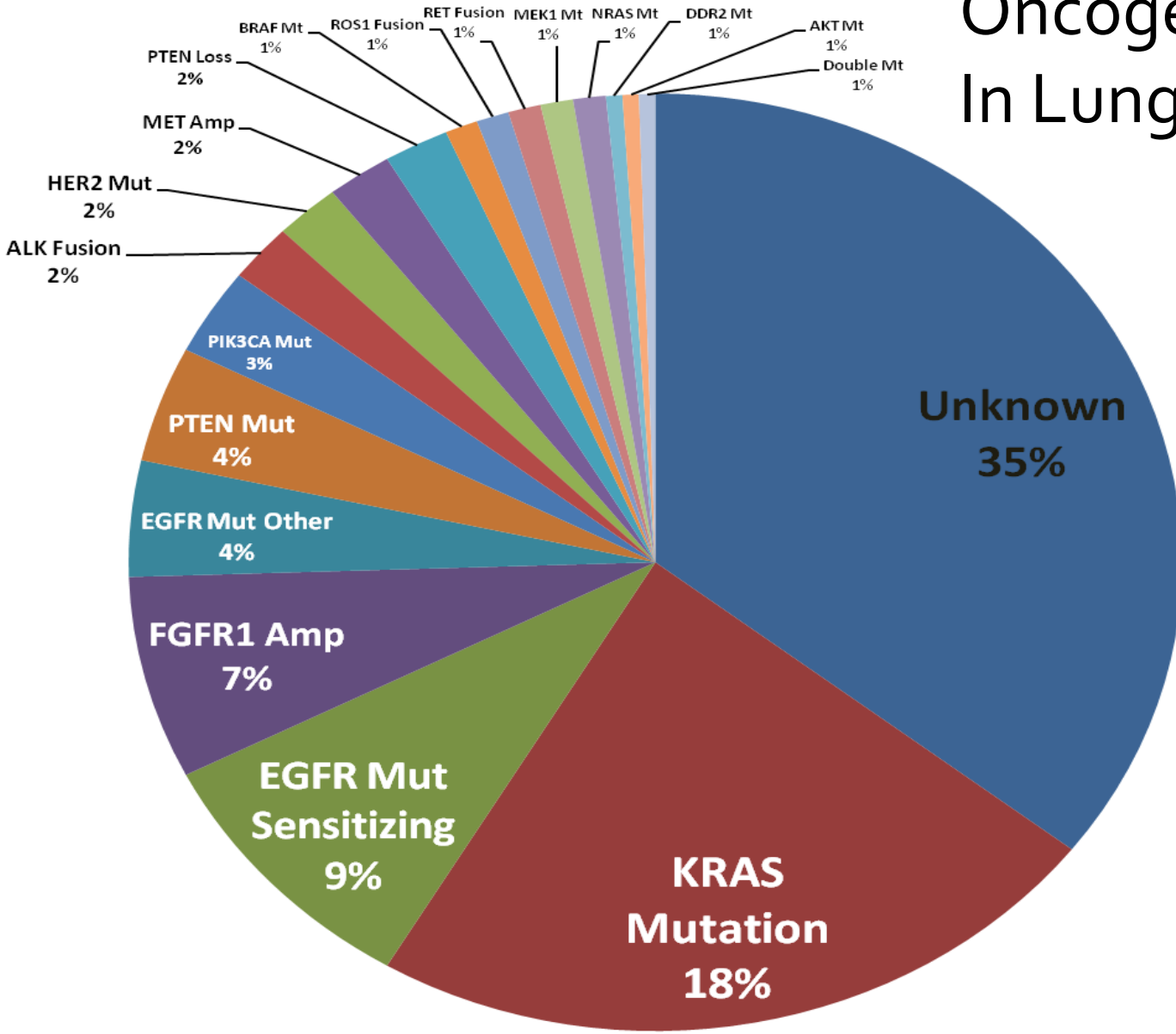
Oncogenic Drivers In Lung Cancers



- Unknown
- KRAS Mt
- EGFR Mt Sn
- FGFR1 Amp
- EGFR Mt Other
- PTEN Mt
- PIK3CA Mt
- ALK Fusion
- HER2 Mt
- MET Amp
- PTEN Loss
- BRAF Mt
- ROS1 Fusion
- RET Fusion
- MEK1 Mt
- NRAS Mt
- DDR2 Mt
- AKT Mt
- Double Mt

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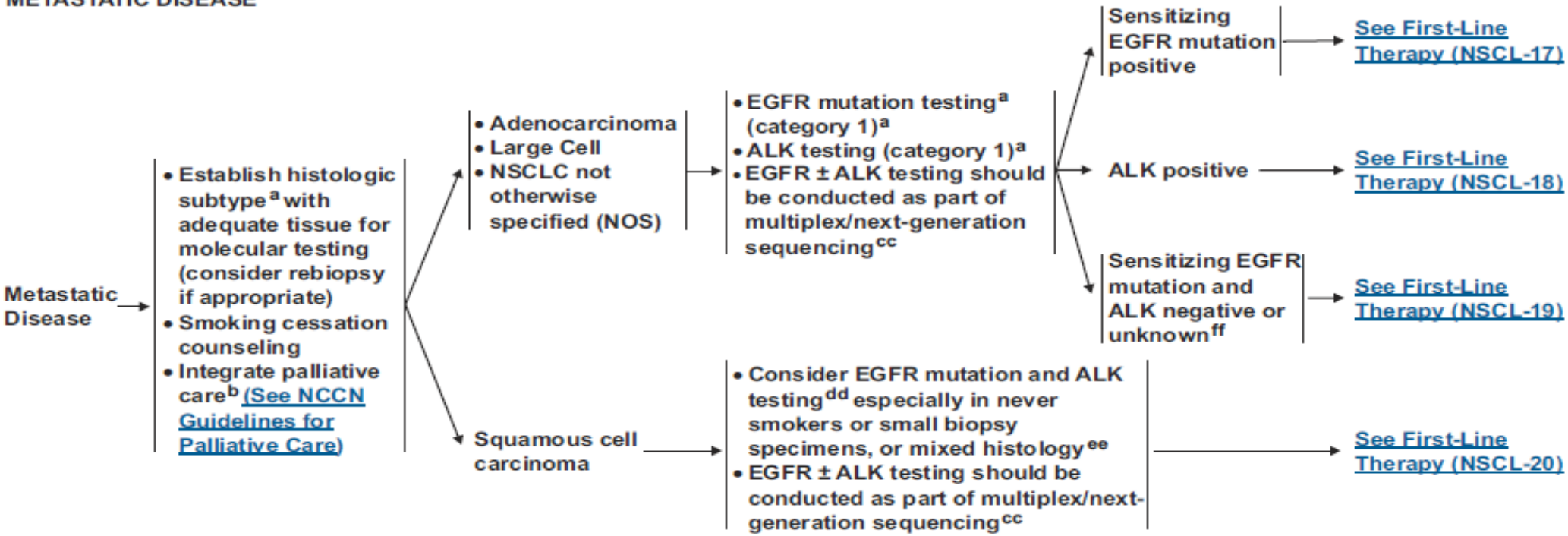
NCCN Guidelines Version 1.2014
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

SYSTEMIC THERAPY FOR METASTATIC DISEASE

HISTOLOGIC SUBTYPE



[a] See Principles of Pathologic Review (NSCL-A).

[b] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[cc] See Targeted Agents for Patients with Other Genetic Alterations (NSCL-H).

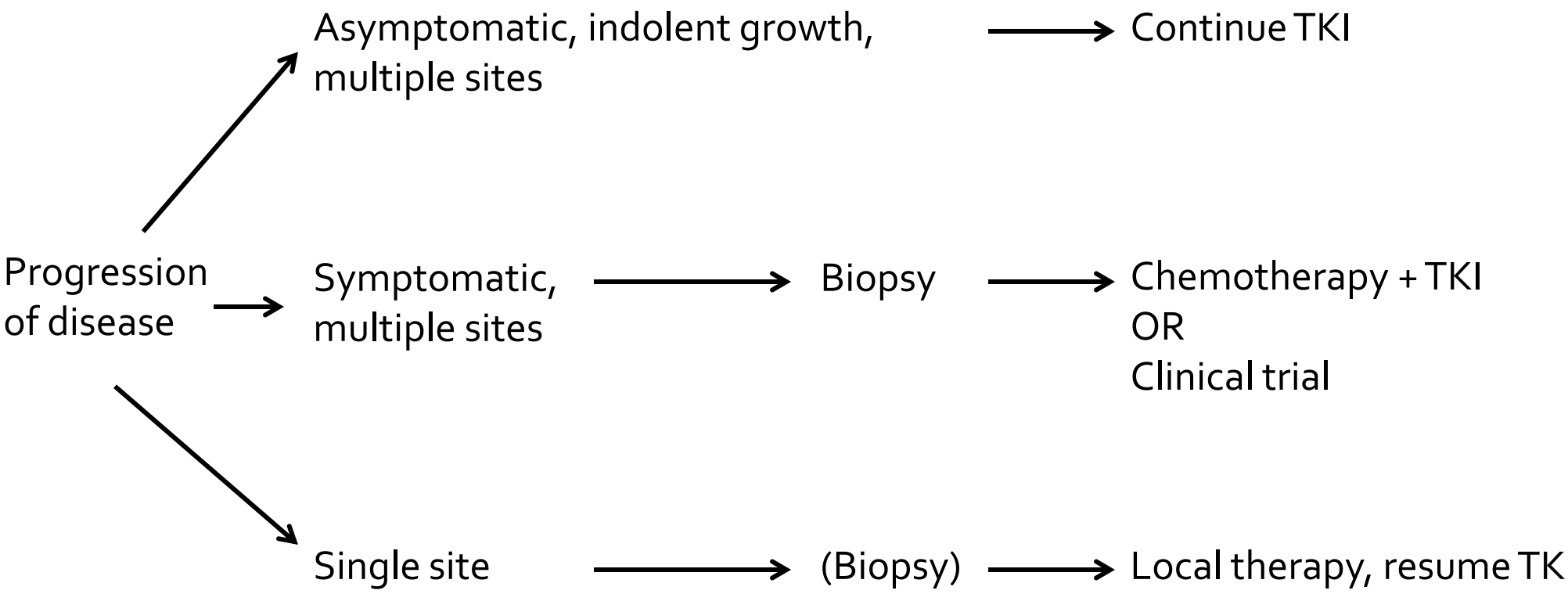
[dd] In patients with squamous cell carcinoma, the observed incidence of EGFR mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

[ee] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with EGFR mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther Published on-line August 14, 2012.

[ff] Consider ROS1 testing; if positive, may treat with crizotinib. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.

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

Managing Acquired Resistance to Tyrosine Kinase Inhibitor (TKI)Therapy of Oncogene-Driven Lung Cancers



Yu, J Thorac Oncol 2013

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Oncogene Dependence

Addiction to Oncogenes—the Achilles Heal of Cancer

I. Bernard Weinstein

…cancer cells are often "addicted to" (that is, physiologically dependent on) the continued activity of specific activated…oncogenes for maintenance of their malignant phenotype.

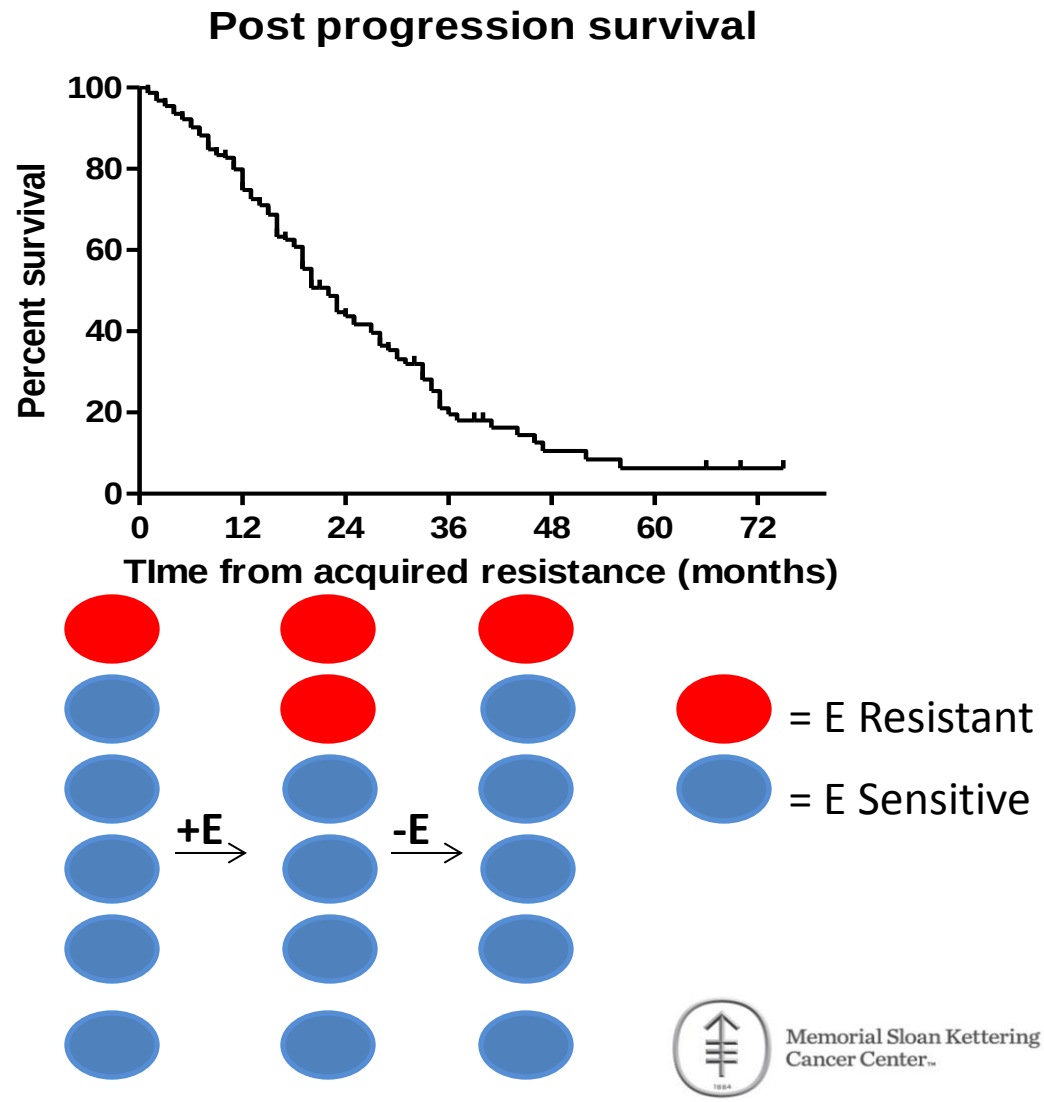
Science, 2002

At the development of EGFR TKI acquired resistance:

- All Cells Remain Oncogene – Addicted
- T790M found in few cells, small fraction of total alleles
- Most cells remain sensitive

Rationale for Continued EGFR Inhibition

- Majority of patients continue EGFR TKI at progression with excellent outcomes
- Coexistence of sensitive and resistant tumor clones
- Avoidance of disease "flare" (23%)



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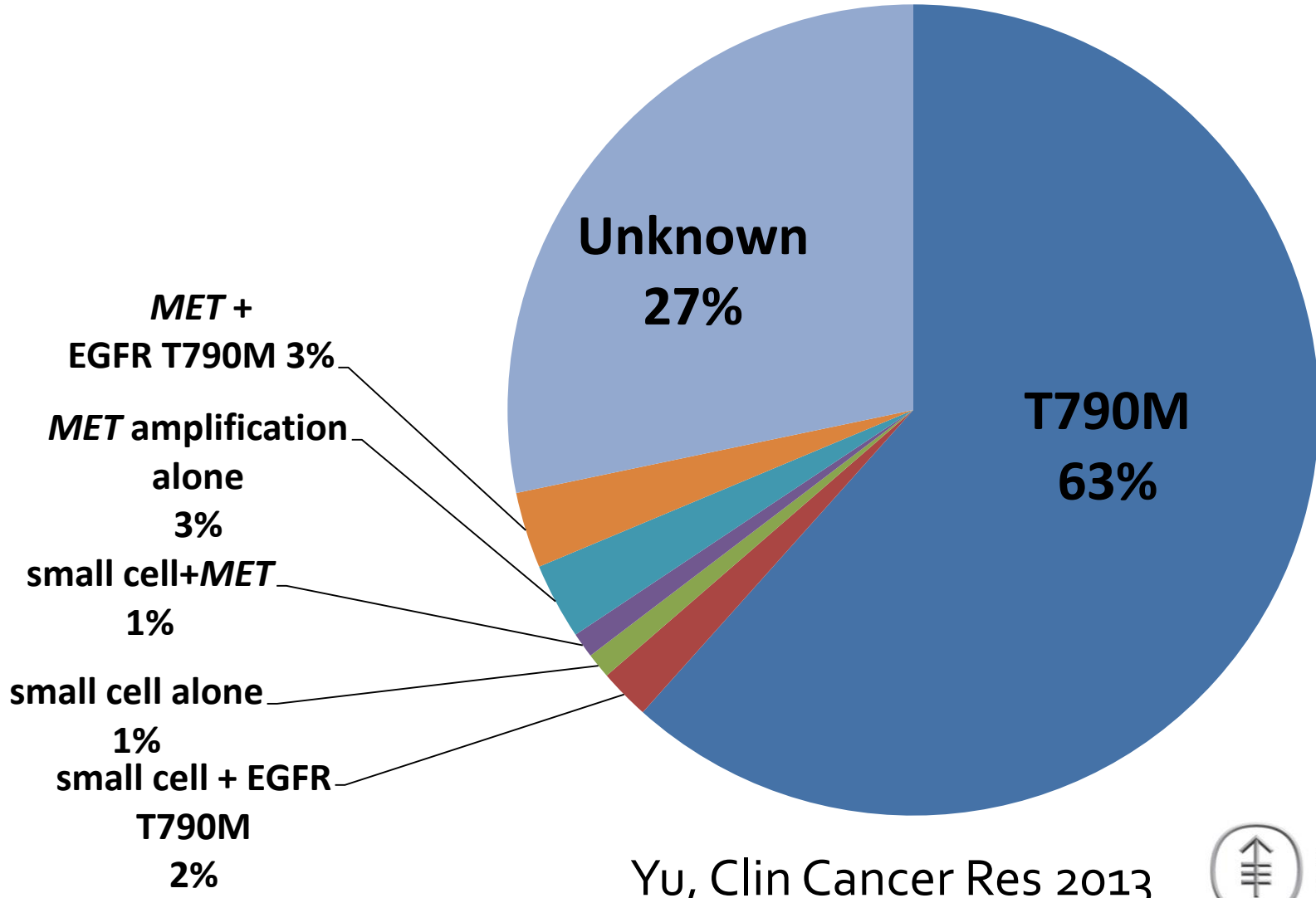
Yu, IASLC 2012
Chaft, CCR 2011
Chmielecki, Sci Transl Med 2011

Look to Mechanisms of EGFR TKI Acquired Resistance to Choose Systemic Therapies



Yu, Clin Cancer Res 2013

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Disease "flare" post-TKI in *EGFR*-mutant lung cancers with AR

- *Pts with EGFR*- mutant cancers on clinical trials for treatment of AR
- "Flare" defined as hospitalization or death during TKI washout (7-21 days)
- 14 of 61 pts (23%, 95% CI 14-35%) experienced a flare
- Median time to flare was 8 days (range 3-21)
- Characteristics associated with flare:
  - Shorter TTP on TKI (Median 9 vs 15 mo, p=0.002)
  - Pleural disease (p=0.02) or CNS disease (p=0.01)
- Flare was not associated with T790M, type *EGFR* mutation, or prior cytotoxic chemotherapy

Chaft Clin Cancer Res 2011

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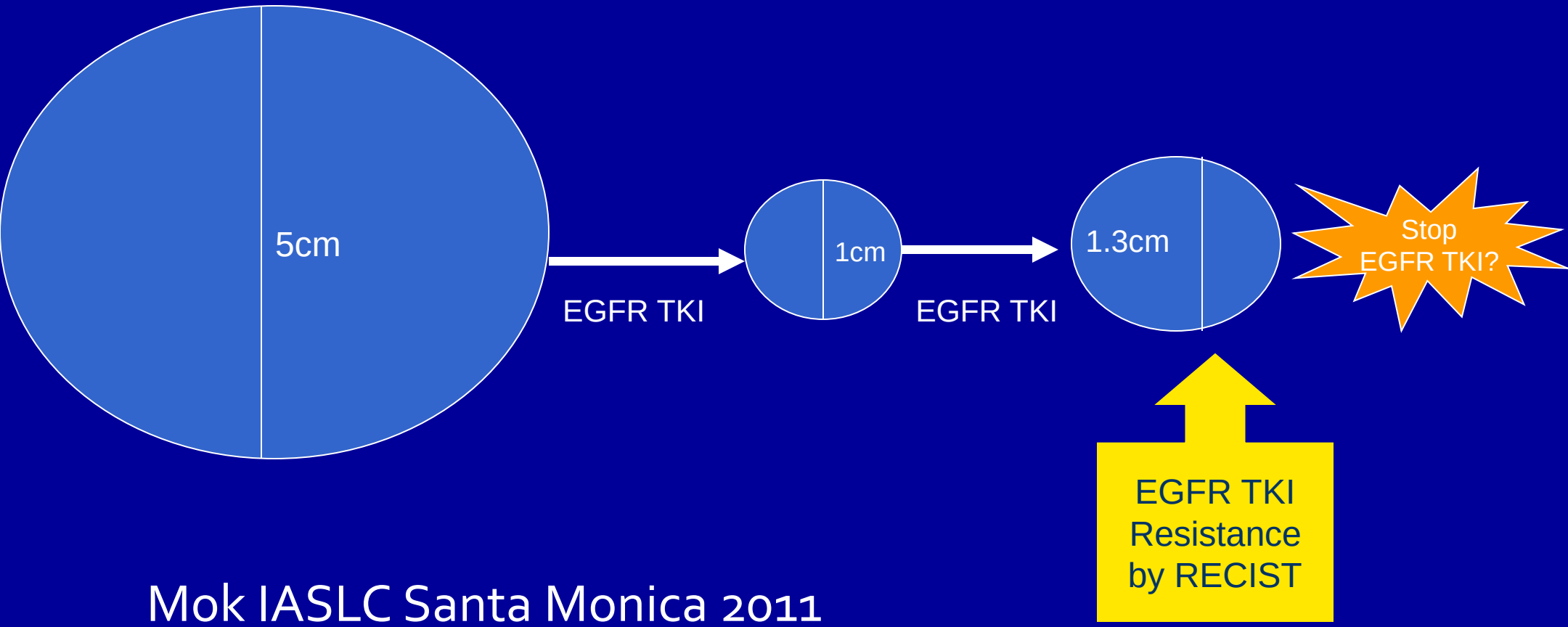
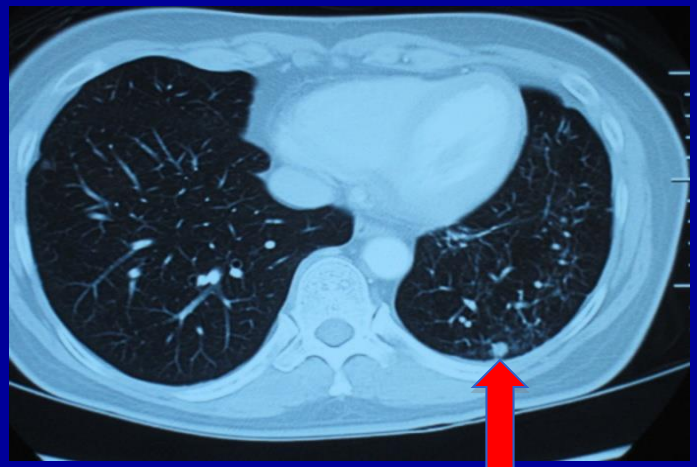
RECIST Criteria for Progression
A Signal to Stop the EGFR TKI?



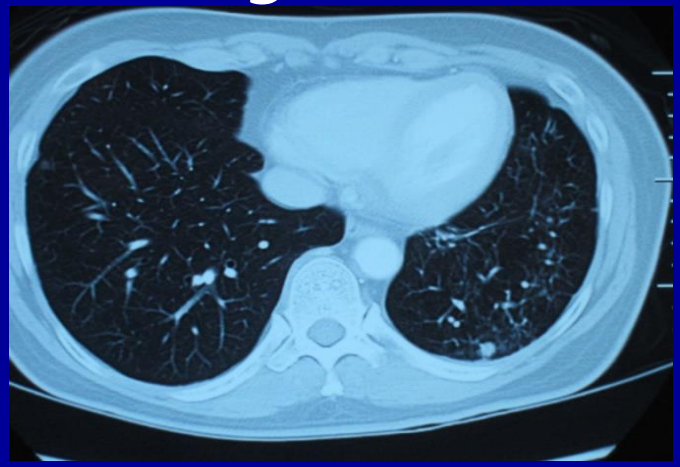
Mok IASLC Santa Monica 2011

Patient treated by Tony Mok with gefitinib for exon 19 *EGFR*-mutant lung cancer since 2005

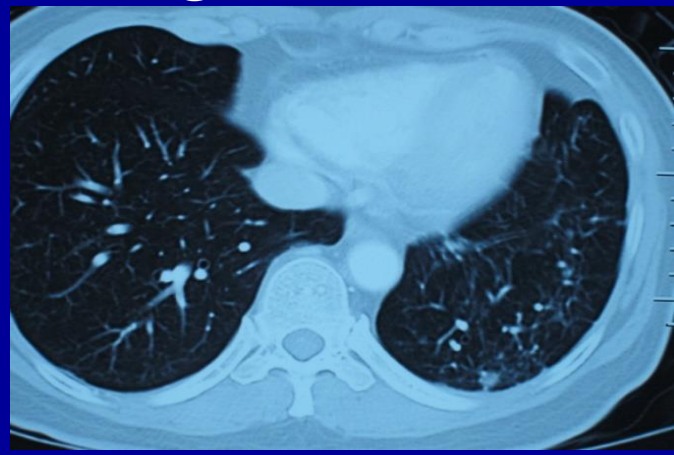


Aug 2008

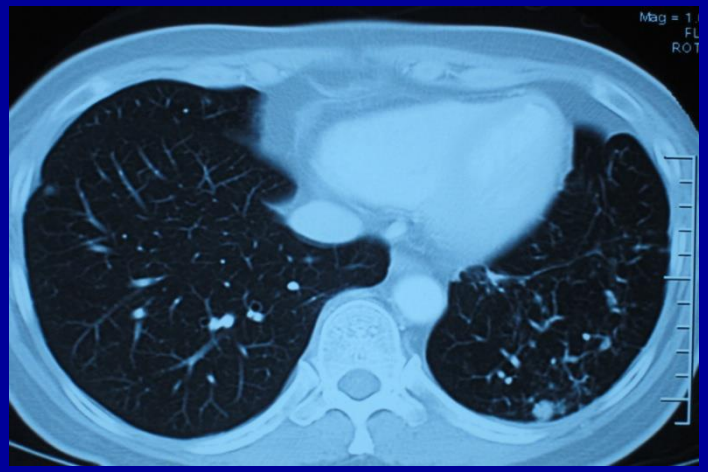
RECIST PD



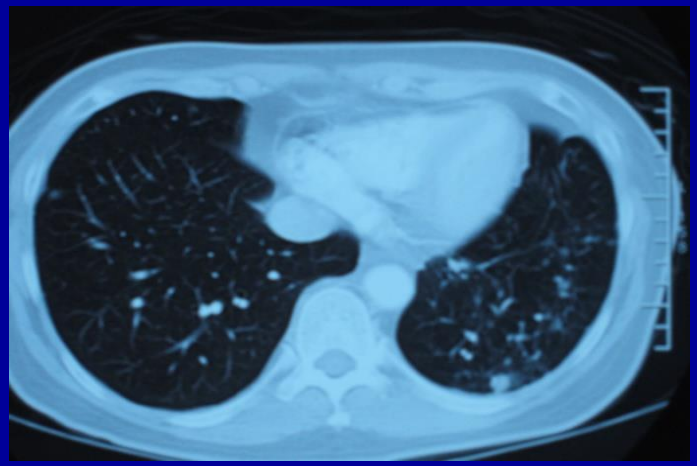
Oct 2008



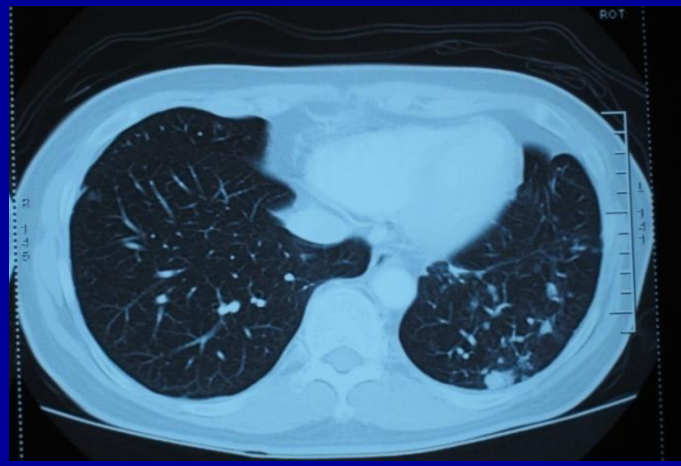
Apr 2009



Aug 2009

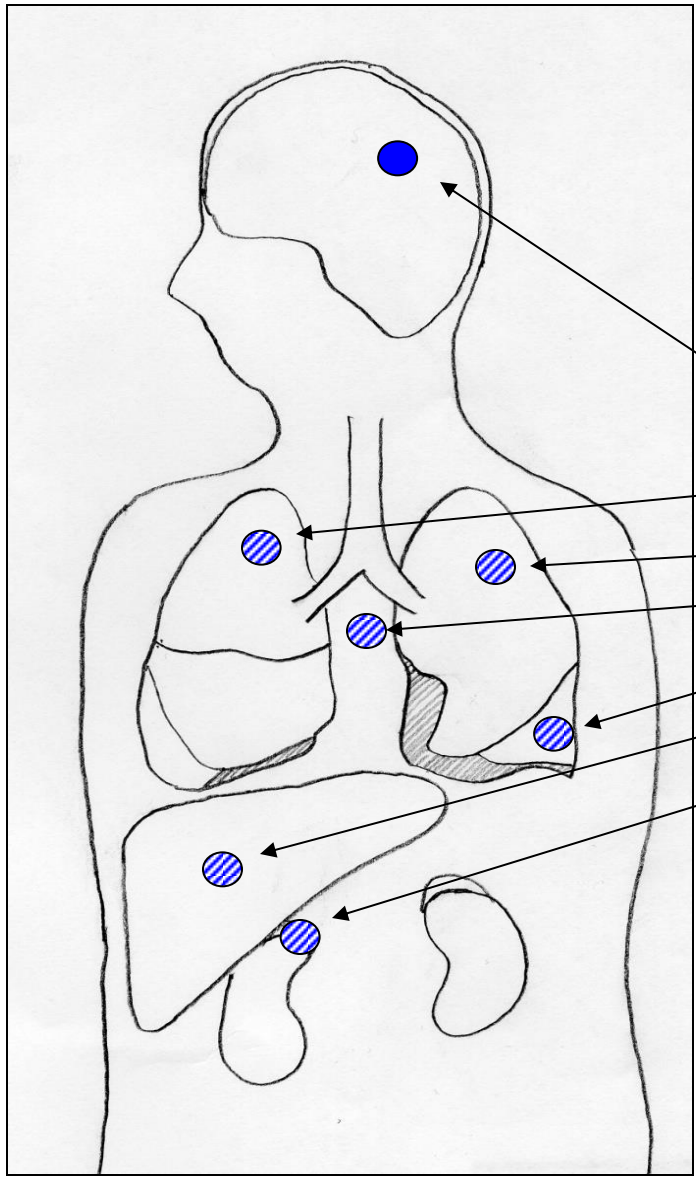


Dec 2009



May 2010

Analysis at Autopsy: *EGFR T*790M Found Everywhere but the Central Nervous System



Brain
RUL
LUL
Thoracic vertebra
LLL
Liver
R adrenal

L747-E749;A750P only

L747-E749;A750P + T790M

Balak Clin Cancer Res 2006

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The Central Nervous System as a ‘Sanctuary’ Site

- High incidence of disease recurrence in the CNS after initial response to gefitinib (Omuro et al, ’05)
- In patients on 250 mg po qd, blood levels = 584 nM (FDA ’02)
- In a patient with acquired resistance on 500 mg po qd, CSF level = 6.15 nM; whereas visceral sites had EGFR T790M, the brain lesions did not (Jackman et al, ‘06)
- It is plausible that:
  - EGFR T790M may not be selected for in CNS
  - EGFR L858R harboring cells could expand in CNS
- Implications:
  - Need better CNS prophylaxis and/or
  - Need better tissue penetration of drug in brain

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 EGFR TKI Acquired Resistance

Methods

Retrospective review of #04-103, other biospecimen registries (#06-107, #92-055)

EXCLUDE

1. Pts with local therapy prior to AR
2. Pts with CNS directed local therapy

Identify patients with EGFR mutant lung cancers with AR to EGFR TKIs who received local therapy

COMPARE

Patients with EGFR mutant lung cancers who did not receive local therapy in the AR setting

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Management of Central Nervous System Metastases

42 of 184 (23%) of patients with acquired resistance to EGFR TKIs had brain metastases and underwent various interventions including surgical resection (N=8), Stereotactic Radiosurgery alone (N=10), and WBRT (N=28). As local therapy for brain metastases is considered standard of care, local therapies to brain metastases were not included in our analysis.

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Local Therapy for Oncogene-Driven Lung Cancers

Patients

	Local therapy pts N=18	Systemic therapy pts N=166	P value
Site of metastatic disease			
Lung/Lymph node	14/8	139/50	0.59
Brain	2	42	
Bone/Visceral	4/2	65/32	
EGFR mutation type- (%)			
Exon 19 deletion	14 (78)	109 (66)	0.63
Exon 21 L858R	4 (22)	53 (32)	
Other	0	4 (2)	
Initial EGFR TKI TTP (months)			
Median (range)	19 (5-33)	12 (2-73)	0.089
Resistance mechanism-no (%)			
T790M	11 (61)	84 (51)	0.63
MET amplification	1 (6)	5 (3)	
Small cell histology	1 (6)	3 (2)	
Unknown	5 (27)	74 (44)	

Yu, J Thorac Oncol 2013

Outcomes for Individual Patients After Local Therapy

Table 3: Outcomes for individual patients after local therapy

Patient	Intervention	Time to Progression (months)	Time to treatment change (months)	Time to death (months)
1	Lung-lobectomy	1+*	1+	1+
2	Lung-SRS**	2+	2+	2+
3	Adrenalectomy	4+	4+	4+
4	Lymph node (mediastinal and supraclavicular)-RT**	3	4	5+
5	Lung-pneumonectomy	2	8	8
6	Lung-RFA	2	3	18
7	Lung-RFA	4	22+	22+
8	Lung-lobectomy	25+	25+	25+
9	Lung-RT**	9	9	26
10	Lung-lobectomy	15	16	26
11	Adrenalectomy	1	4	28
12	Lung-pneumonectomy	21	21	29
13	Lung-pneumonectomy	28	29	32+
14	Lung-wedge	2	6	42
15	Lung-lobectomy	12	30	43+
16	Lung-lobectomy	45+	45+	45+
17	Lung-lobectomy	51	54	64
18	Lung-lobectomy	10	23	65+

*+ indicates patients who have not died or progressed during study follow up
** Lung SRS was 4500cGy/5 fractions, Lung RT was 6000cGy/3 fractions and Lymph node RT was 5000cGy/25 fractions

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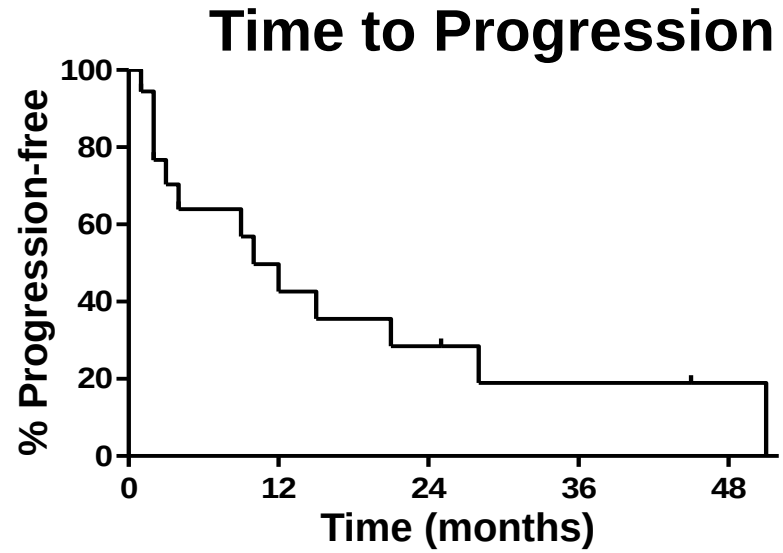
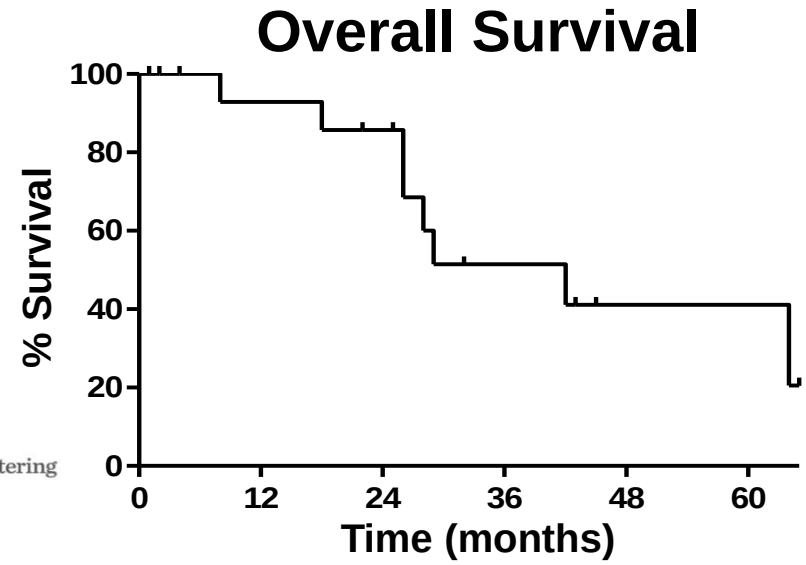
Local Therapy for Oligo-Progression Outcomes

- 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).





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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)

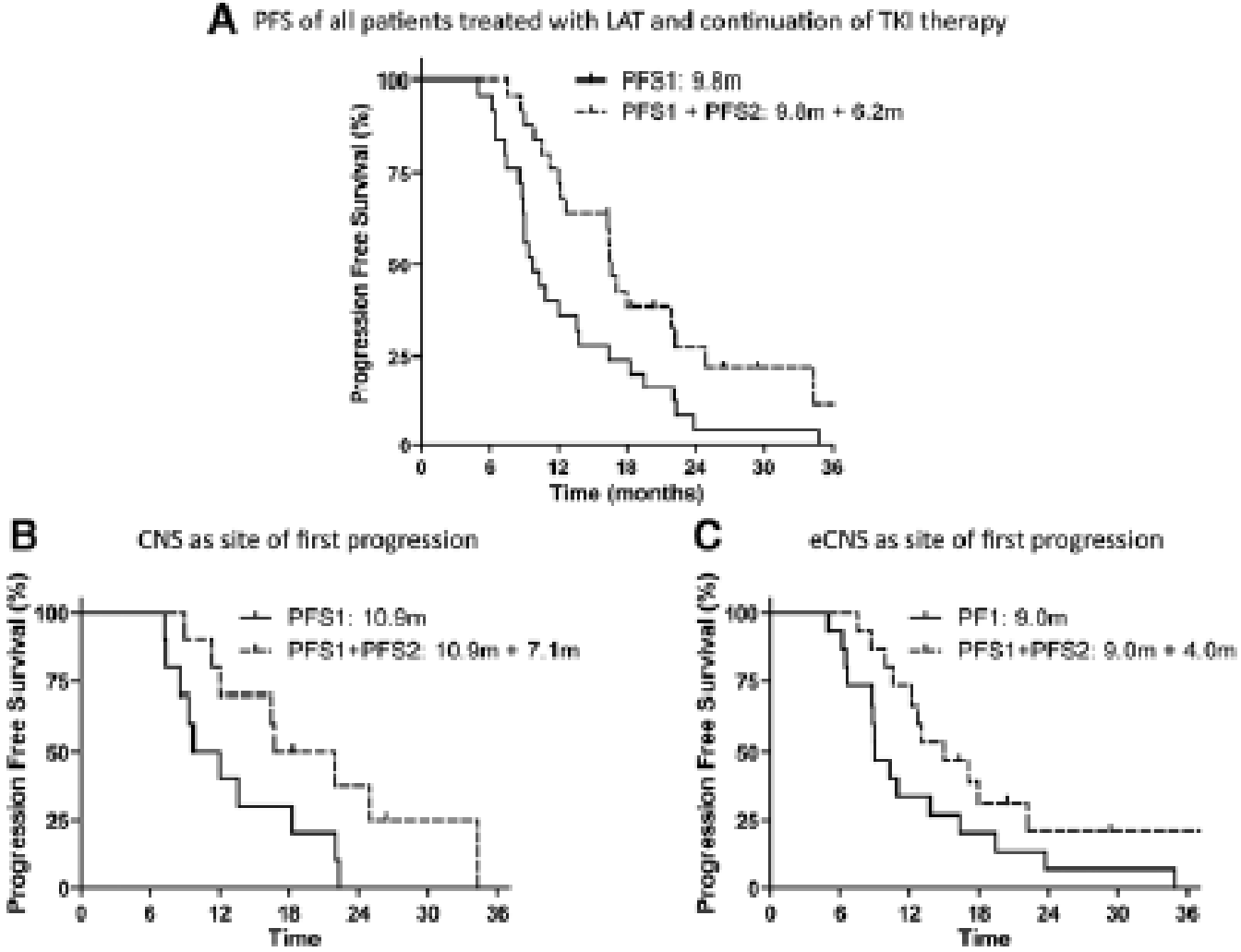


FIGURE 1. *A*, PFS1 and PFS1+PFS2 survival curves of all 25 patients treated with LAT. *B*, Ten patients treated with LAT who first progressed only in the CNS. *C*, Fifteen patients treated with LAT who first progressed in extra-CNS locations, including three patients with simultaneous CNS and eCNS progression. 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 J Thorac Oncol 2012

TABLE 5. Suggested Criteria for Considering Local Ablative Therapy of Oligoprogressive Disease and Treatment with a TKI beyond Progression Includea

1. *ALK* positive or *EGFR*-mutant metastatic non–small-cell lung cancer
2. Relevant TKI (e.g., crizotinib or erlotinib) is well tolerated
3. Oligoprogressive disease on TKI therapy, defined as:

   CNS progression without leptomeningeal disease amenable to WBRT, SRS, or surgical resection.

   Progression in ≤ 4 extra-CNS sites amenable to SBRT, XRT, or surgical resection.

[a]Based on the practices within this study.

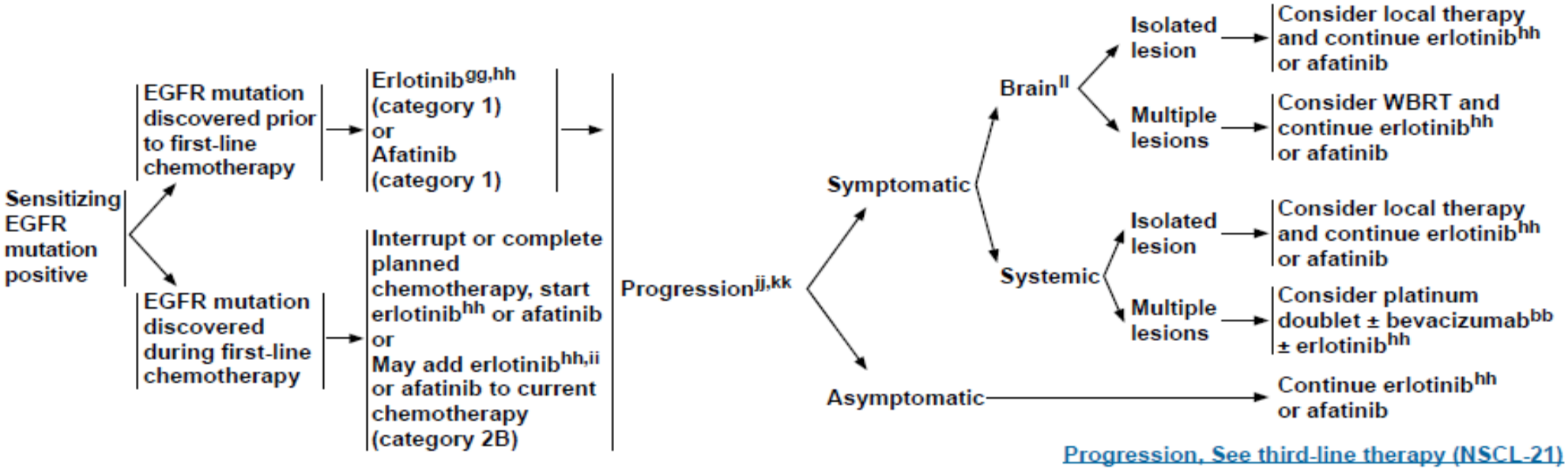
WBRT, whole brain radiation therapy; SRS, stereotactic radiosurgery; SBRT, stereotactic body radiation therapy; XRT, conventionally fractionated radiation therapy; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor recepetor.

Weickhardt J Thorac Oncol 2012

Just when you thought you knew what to do ….
New drugs likely to modify treatment strategies

- ALK-positive lung cancers
  - Ceritinib
  - AP26113
  - Alectinib
- EGFR-positive lung cancers
  - Pulse Dosing with erlotinib and dacomitinib
  - Afatinib + Cetuximab (“Afacet”)
  - Mutation-Specific Kinase Inhibitors
    - ASP 8273
    - AZD9291
    - CO-1686
    - EGF816
    - HM 61713

ADENOCARCINOMA, LARGE CELL, NSCLC NOS: SENSITIZING EGFR MUTATION POSITIVE[a]

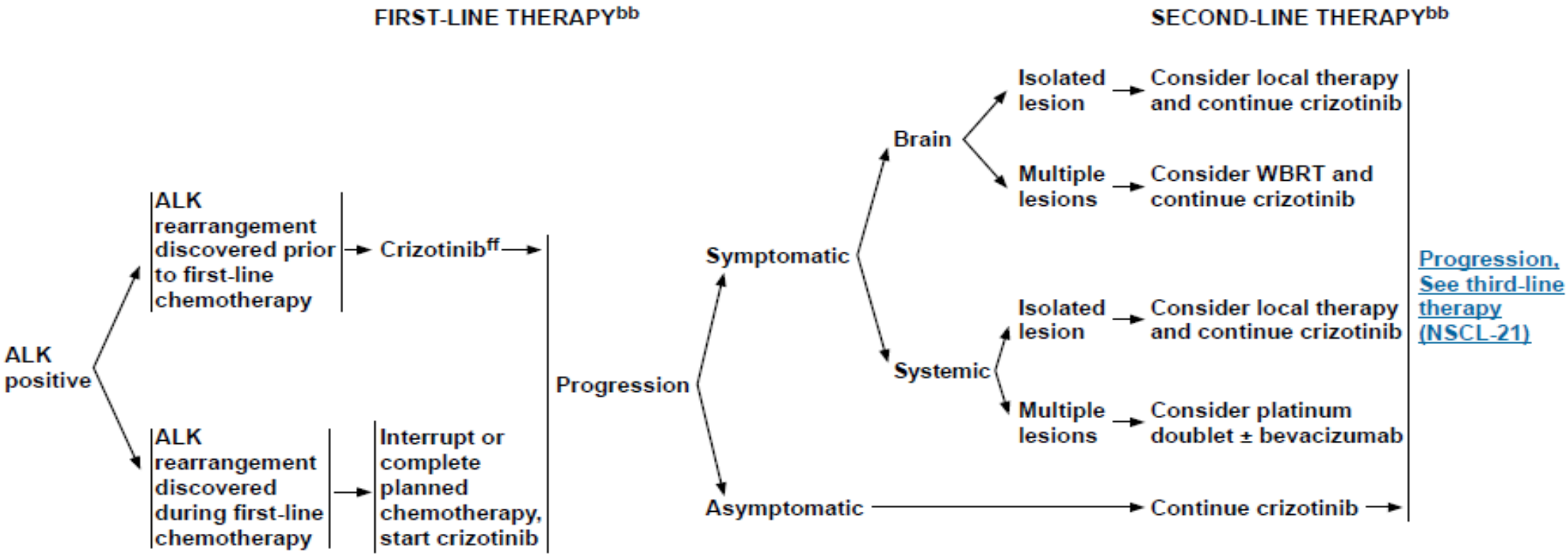


Progression, See third-line therapy (NSCL-21)

[a] See Principles of Pathologic Review (NSCL-A).
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[gg] For performance status 0-4.
[hh] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[ii] Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who are never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol 2012;30:2063-2069.
[jj] Biopsy on progression to determine mechanism of acquired resistance, because proportion of patients will transform to SCLC at progression.
[kk] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[ll] Consider pulse erlotinib for carcinomatosis meningitis.
[mm] Afatinib appears to have some efficacy in patients who progressed on EGFR therapy. Miller VA, Hirsh V, Cadrenal J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.

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

ADENOCARCINOMA, LARGE CELL, NSCLC NOS: ALK POSITIVE[a]



[a] See Principles of Pathologic Review (NSCL-A).
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ff] Consider ROS1 testing; if positive, may treat with crizotinib. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.

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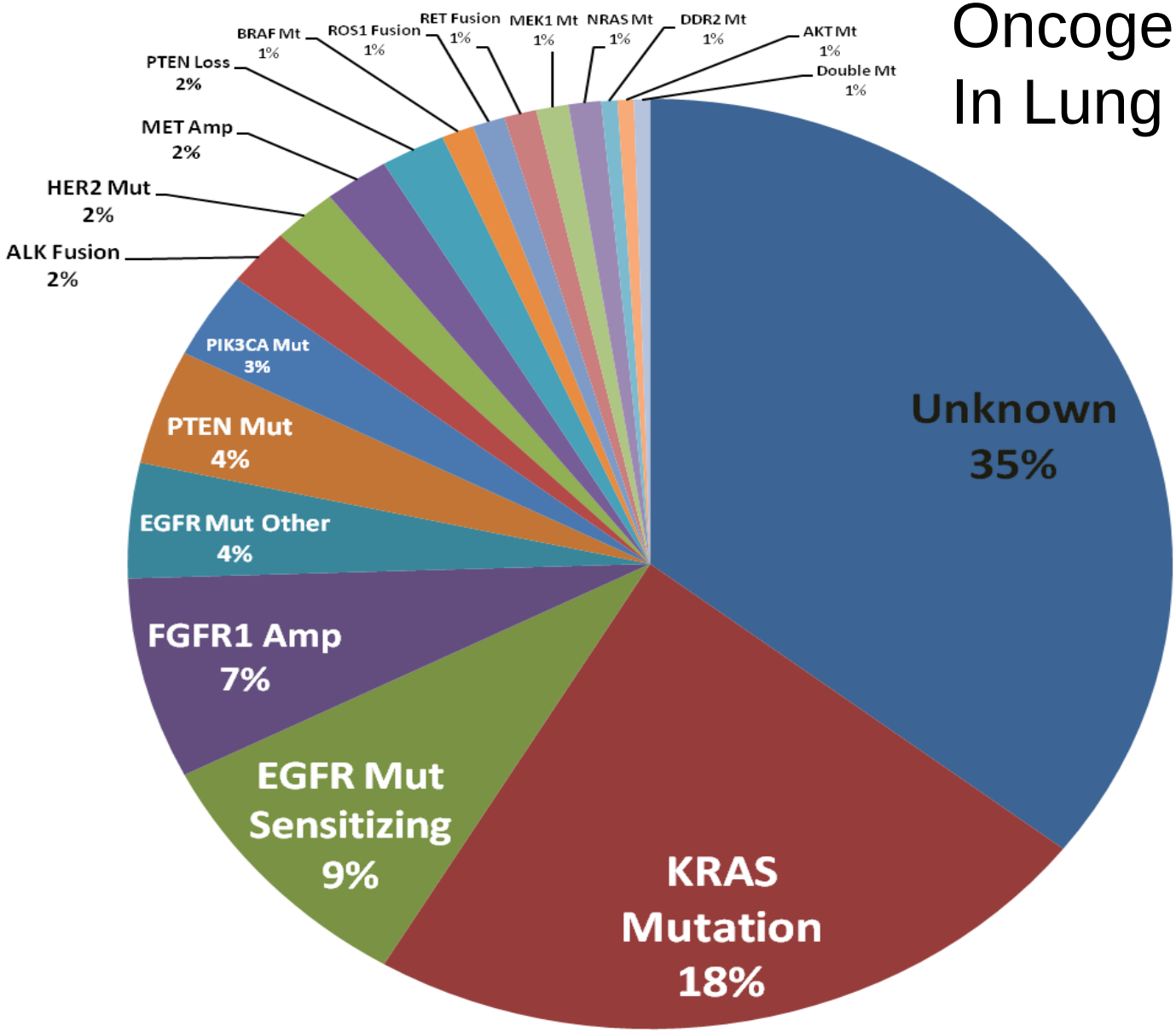
Management of Oligo-Progression in Patients with Oncogene-Driven Lung Cancers

Conclusions

- Oncogene-driven lung cancers are unique
- At 1st progression, all cells remain oncogene addicted and the vast majority of cancer cells remain sensitive the 1st TKI used
- Solitary brain metastases require special consideration
- Some resistant cells (like EGFR *T790M*) slower growing
- Resist RECIST alone to decide to change therapies
- Symptoms are the best guide to decide when to change
- Strategy will be modified by next generation kinase inhibitors
- Oncogene –driven lung cancers the vanguard of personalized care

Oncogenic Drivers In Lung Cancers



- Unknown
- KRAS Mt
- EGFR Mt Sn
- FGFR1 Amp
- EGFR Mt Other
- PTEN Mt
- PIK3CA Mt
- ALK Fusion
- HER2 Mt
- MET Amp
- PTEN Loss
- BRAF Mt
- ROS1 Fusion
- RET Fusion
- MEK1 Mt
- NRAS Mt
- DDR2 Mt
- AKT Mt
- Double Mt

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