# Current Status of Targeted Therapy for NSCLC

James R Jett, MD

National Jewish Health

Denver, Colorado

# Potential Conflicts of Interest

- Served on advisory board for:

  Genentech, Pfizer and BMS -- targeted therapy agents

  Oncimmune--biomarkers lung cancer: Research grant pending approval; iSense: Research grant pending

# IASLC/ATS/ERS International Classification of Lung Adenocarcinoma

www.JTO.Org

Travis et al J Thorac Oncology 2011; 6:244-283

National Jewish Health

# Specimen Handling for Molecular Testing

- Molecular Testing of NSCLC is Hampered by Small Diagnostic Specimen
- Limited Tissue is Further Reduced by Diagnostic IHC Testing and Aggressive Tissue Block Facing
- "Molecular Only" Testing Offers a High Success Rate at University of Colorado

Aisner et al. *J Thorac* Oncol 2012; 7:S223 (Abstract #130)

# Suitability of EBUS-TBNA Samples

- Final Diagnosis by EBUS in Whom Subtype Was Classified 77% (CI 73-80%)
  - Rate of NOS Was Significantly Reduced When IHC Performed (OR 0.50)
- EGFR Mutational Analysis Was Possible in 90% of the Patients (Adequate Samples)
  - These Were Experienced EBUS Centers

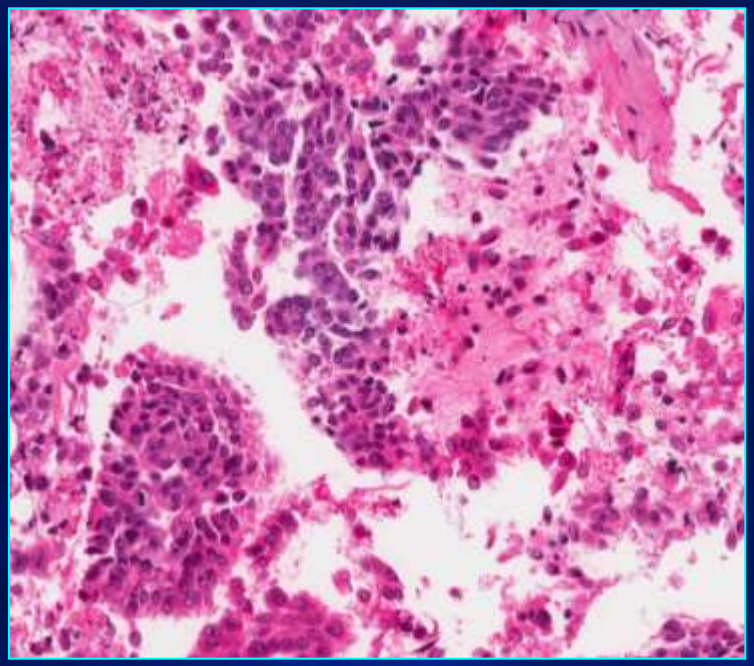
Navani et al. *AJRCCM* 2012; 186:255-260

# Transthoracic Core Needle Biopsy BATTLE Lung Trial

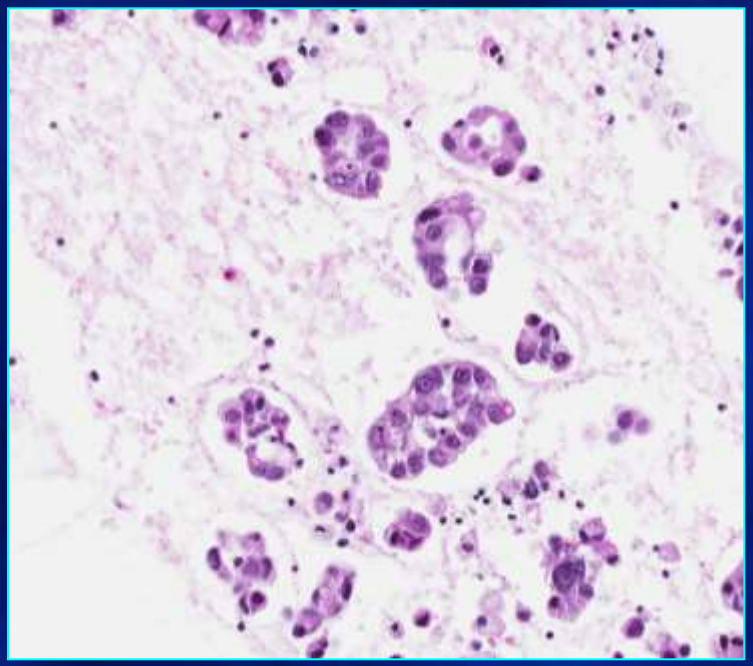
- 20G needle Bx in 151 NSCLC patients screened for trial
- 83% specimens were adequate for biomarker testing (11 markers)
- Metastatic lesions were 5X more likely to yield diagnostic tissue
- Pneumothorax in 15%; chest tube 9%

# Use of Cytological Material for Molecular Diagnosis of Lung Cancer

## Cell Block - Histology Sections



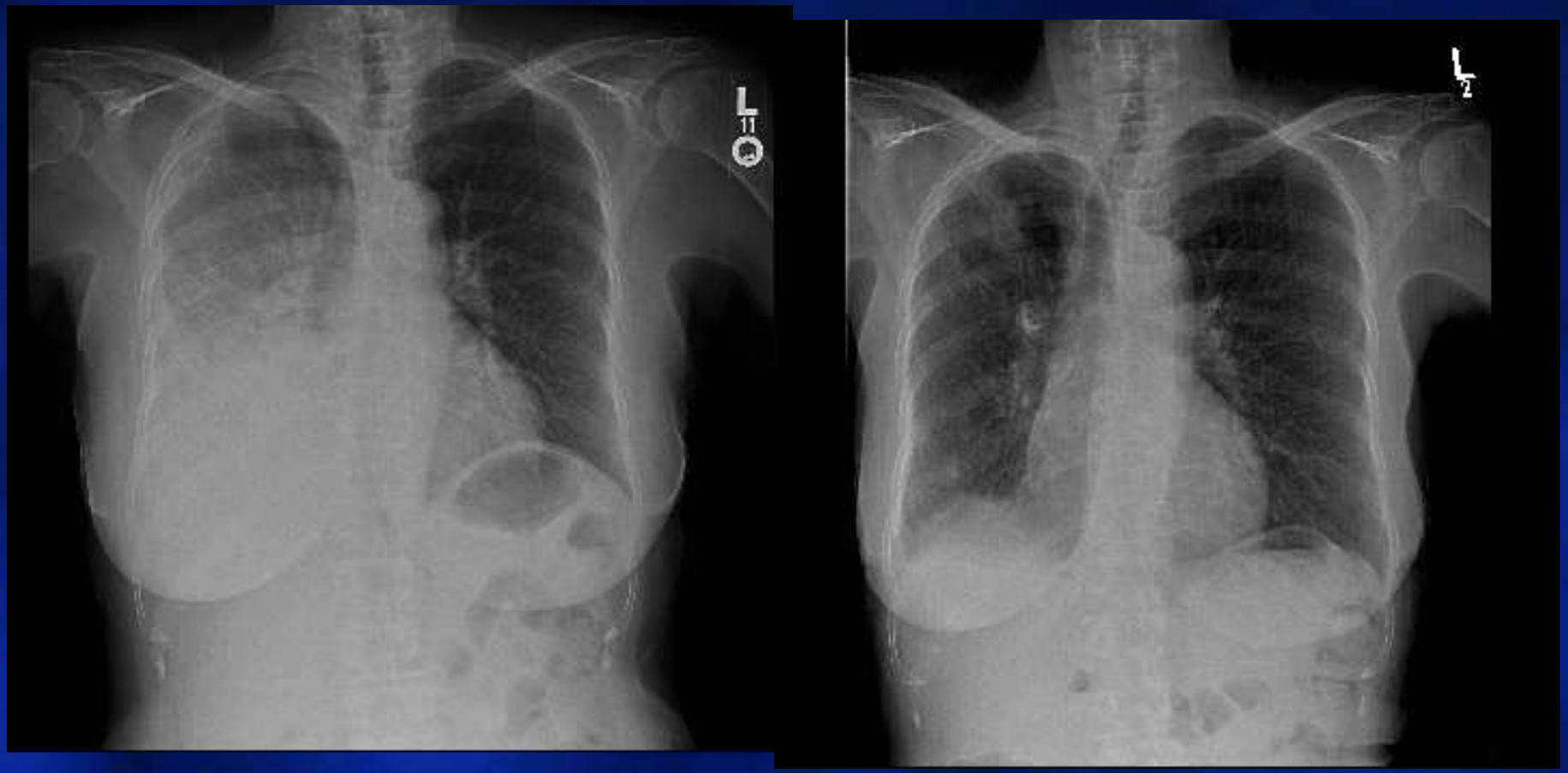
Fine Needle Aspiration



Pleural Fluid

# EGFR Mutations in Tyrosine Kinase Domain

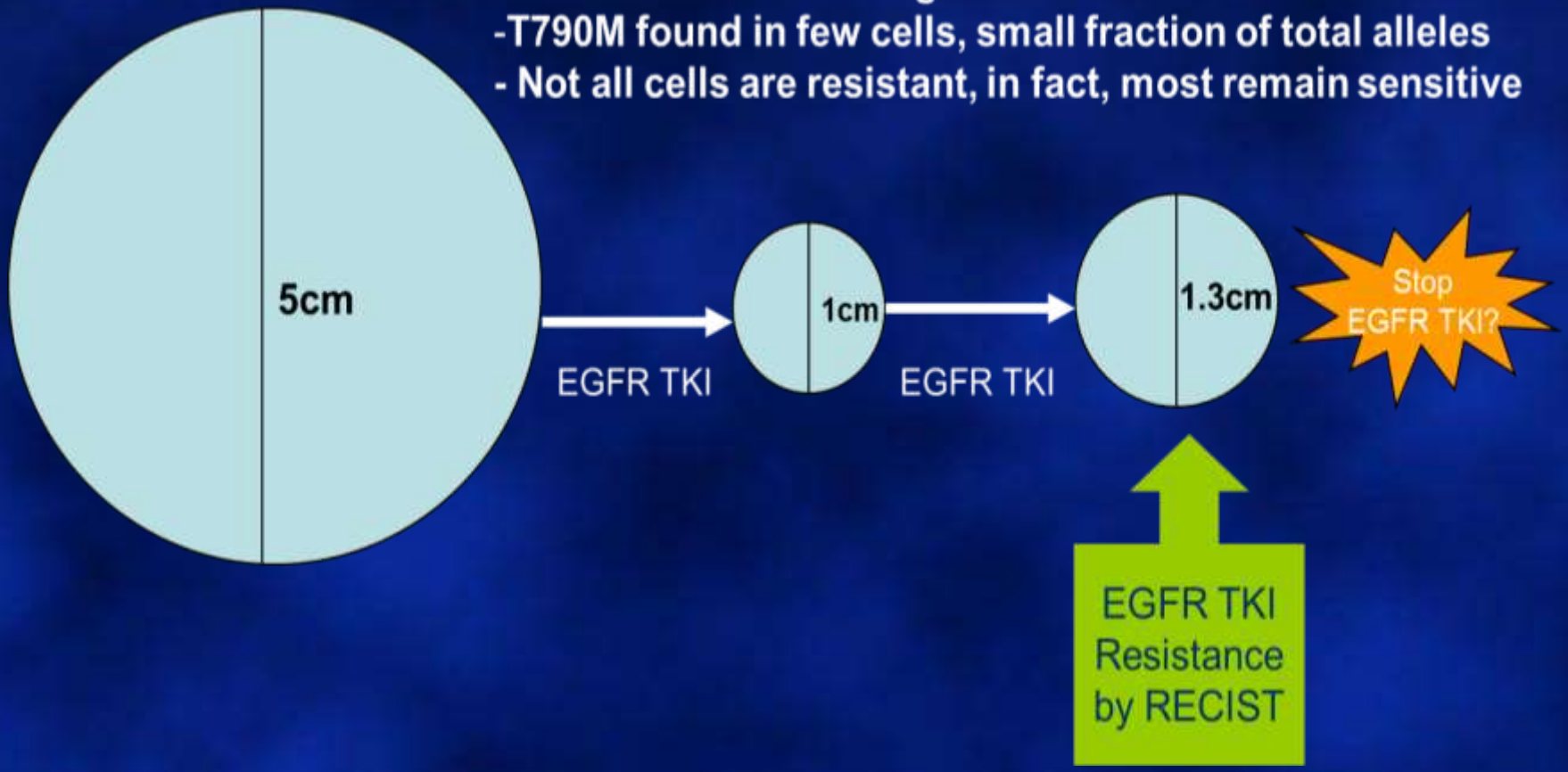
- 90% of lung cancer EGFR mutations
  - Exon 19 deletion LREA sequence (del E746-A750)
  - * Exon 21 mutation; L858R (leucine to arginine substitution)
- Resistant mutation exon 20
  - T790M
  - Exon 20 insertion



# EGFR mutation: Exon 19 deletion

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

At the development of acquired resistance:
-All Cells Remain Oncogene – Addicted
-T790M found in few cells, small fraction of total alleles
- Not all cells are resistant, in fact, most remain sensitive



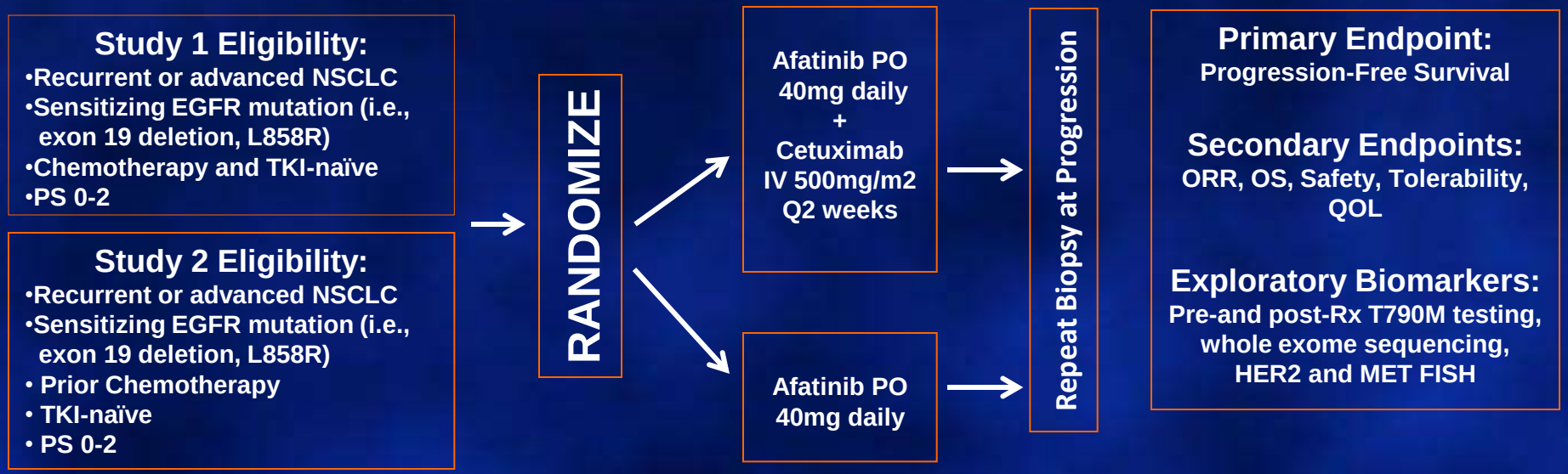

Mok T. Proc IASLC Santa Monica Workshop, 2011

# Continuation of TKI + Local Rx for TKI PD on Erlotinib or Crizotinib

| Study | N pts | PFS1 | PFS2 |
|---|---|---|---|
| Colorado | 25 | 10 | 6.2 |
| MSKCC | 18 | 19 | 10 |

Weickhardt A, et al, Proc ASCO 2012 # 7526
Yu A, et al, Proc ASCO 2012 # 7527

# Randomized trials of afatinib plus cetuximab versus afatinib alone in treatment-naïve and previously treated patients and with advanced, *EGFR* mut+ NSCLC

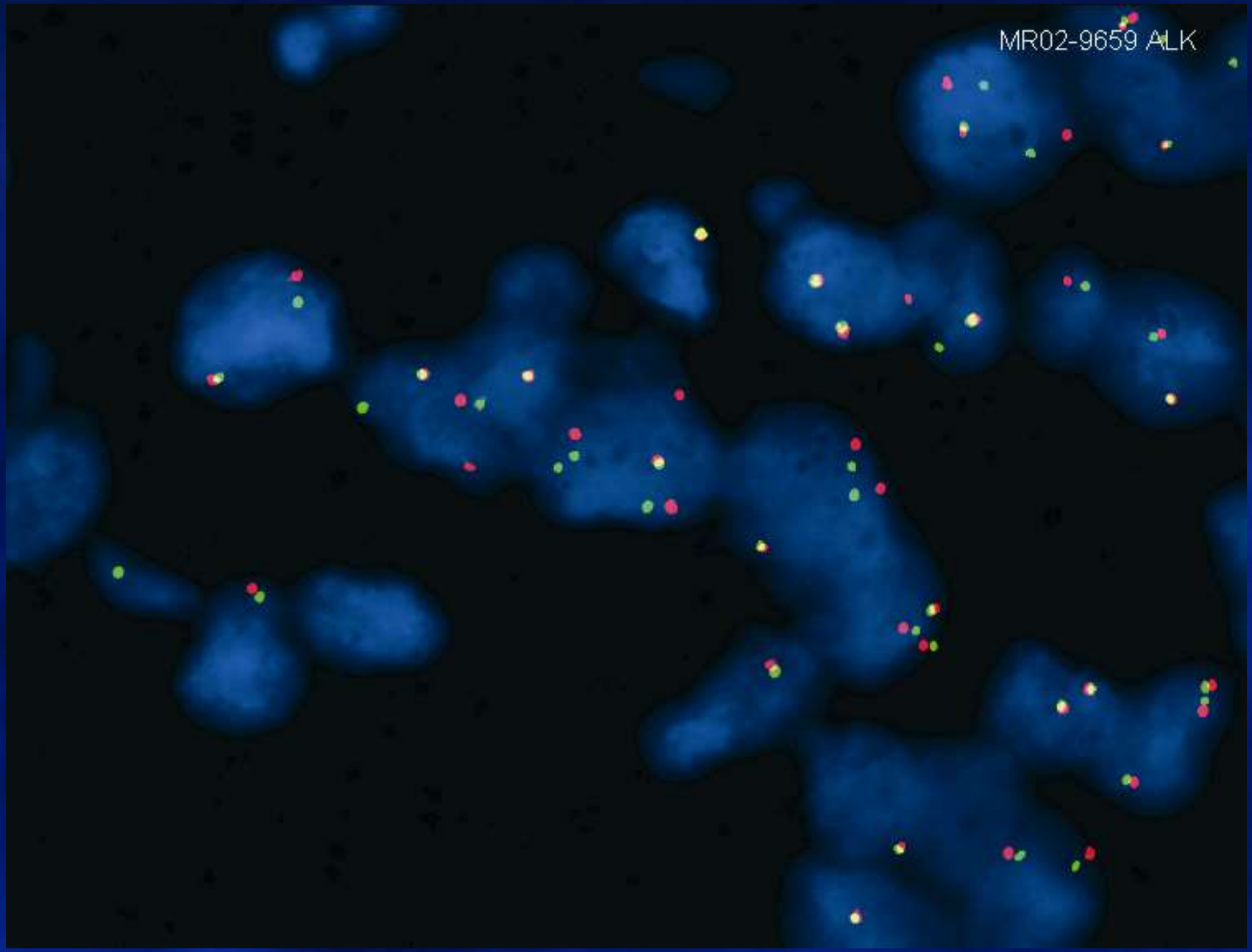



Initial Evaluation:
PET-CT
Brain CT or MRI
ECG, Echo/MUGA
Tumor Molecular Analysis

CT Scans q8 Wks

# Third Generation EGFR TKIs

- Irreversible Binding of Activating and T790M Mutations But Not Wildtype
  - WZ4002 (DFCI) - tool
  - CO-1686 (Clovis) OR=4/6 at highest dose (900mg BID-reformulation ongoing)
  - AP26113 (Ariad) – ALK, too OR 0/3 in T790M
  - TAS-2913 (Taiho)
  - AZD9291 (AZ) Phase 1 ongoing
  - Z650 (HEC Pharma)


MR02-9659 ALK

# EML4-ALK in NSCLC

- Screened 141 NSCLC based on ≥ 2 of following: female, Asian, NS/light smoker, and adenocarcinoma
- 19 of 141 (13%) were ALK mutations
  - 31 (22%) were EGFR mutations
  - 91 (65%) were wild type for both

Shaw et al. J Clin Oncol 2009; 27:4247.

# Preselection Screening for ALK In German Lung Cancer Patients

- Patients were negative for EGFR mutations
- 61 patients; mean age 56; 90% ACA
  - 41% female
- 16% were positive for EML4-ALK
  - 60% female, smoked less and were younger

Tufman et al J Thorac Oncol 2014; 9:109

# FDA Approves Crizotinib (Xalkori): August 26, 2011

- For advanced  or metastatic NSCLC that is ALK transformation positive
- FDA approved Vysis ALK Break apart FISH probe kit (Abbott Molecular, Inc)
- 255 patients; 96% adenoca;95% metastatic; 94% had prior treatment; median age 52 yrs
- ORR was 50% and 61% in 2 studies with MDR of 42 and 48 weeks; only 1% CR
- Mild visual disturbances; G3/4 SAE in 4%

Fatal pneumonitis in 1.6% (1$^{st}$ 2 mos)

# Parallel FISH and IHC Tests of ALK Reveal Major Discordances

- FISH by Abbott BA probe (Vysis) and Dako split probe is Rennes and Bordeaux cohorts respectively (2 probes equivalent in 100)
- IHC assayed in both centers using Abcam (clone 5A4)
  - In Rennes used Ventana automation immunostainer
  - In Bordeaux used Bond-maX automation immunostainer

Cabillic et al March 2014 J Thoracic Onc

# Parallel FISH and IHC Tests of ALK Reveal Major Discordances

- 3244 consecutive NSCLC cases analyzed at two French Centers
- FISH and or IHC was + in 150 (4.6%)
  - Only 80 of 150 were + by both
  - FISH pos ; IHC neg in 36
  - FISH neg; IHC pos in 19
  - FISH noncontributory; IHC + in 15

Cabillic et al J Thorac Oncol 2014; 9:295

# Ongoing Randomized Trials of Crizotinib in ALK + NSCLC

**PROFILE 1007 (N=318)**

- ALK-FISH positive
- 1 prior chemotherapy (platinum-based)

→ RANDOMIZE →

- Crizotinib 250 mg BID (n=159) [continuous]
- pemetrexed 500 mg/m$^2$ or docetaxel 75 mg/m$^2$ (n=159) infused on day 1 of a 21-day cycle

**PROFILE 1014 (N=334)**

- ALK-FISH positive, non-squamous NSCLC
- No prior treatment for advanced disease

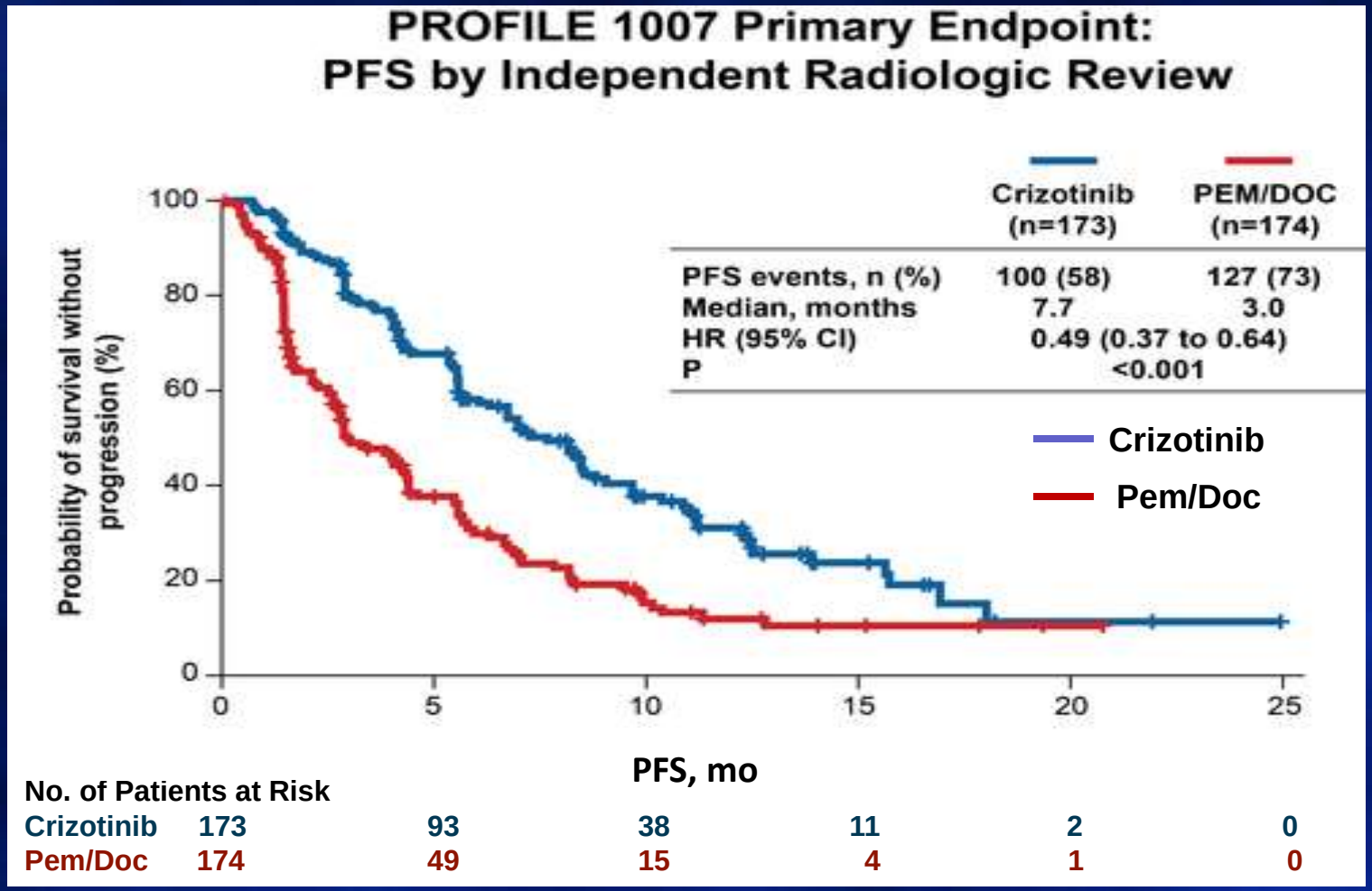
→ RANDOMIZE →

- Crizotinib 250 mg BID (n=167) [continuous]

  Crossover on PD

- pemetrexed/cisplatin or pemetrexed/carboplatin (n=167) infused on day 1 of a 21-day cycle

# Crizotinib vs Chemotherapy




Pem/Doc = pemetrexed/doceteaxel

Shaw A, et al.[24]

# Phase 1/2 Trials of 2nd Generation ALK Inhibitors

| Study | N pts | OR (N) | OR |
|---|---|---|---|
| LDK378 All* | 114 | 66* | 75%* |
| LDK CRZ pre* | 79 | 45* | 78%* |
| AP26113 pre** | 24 | 15 | 73 |
| CH5424802^ | 46 | 39 | 83 |

*ASCO 8010 OR=CR+PR+uPR; **ASCO 8031; ^ASCO 8033 all 2013

**Is there space for second generation inhibitors of EGFR and ALK?**

# ROS1 Receptor Tyrosine Kinase Rearrangement & Crizotinib Rx

- FISH break apart assay: 250mg BID
- 25 treated and evaluable
  - Median age 51; 79% NS; 97% ACA
  - Prior Rx median 1 (range 0-7)
- ORR was 56%; 2CR; 12 PR; 8 stable
  - Median Rx duration 24 weeks
  - 6 months PFS probability 71%

Ou et al J Clin Oncol 2013; 31: abst 8032

# RET Fusions

- About 1% of NSCLC
- KIF5B-RET or
  - CCDC6-RET
- Mutually Exclusive of EGFR, KRAS, and ALK Mutations

*Nature Med* 2012;18:375; 18:378; 18:382

# Strategies for Identifying ROS1 and RET mutations

- Occur in 2,000 to 3,000 ACA per year
- Screened 51 ACA that were negative for EGFR, ALK, KRAS, ROS1
  - 8 patients (15%) had RET fusions
- Screened 35 mutation neg (LCMC), never smokers with ACA
  - RET in 15% and ROS1 in 15%

J Clin Oncol 2013; 31 abstr 8024 (U of CO) and 8067 (MSKCC)

# Vandetanib

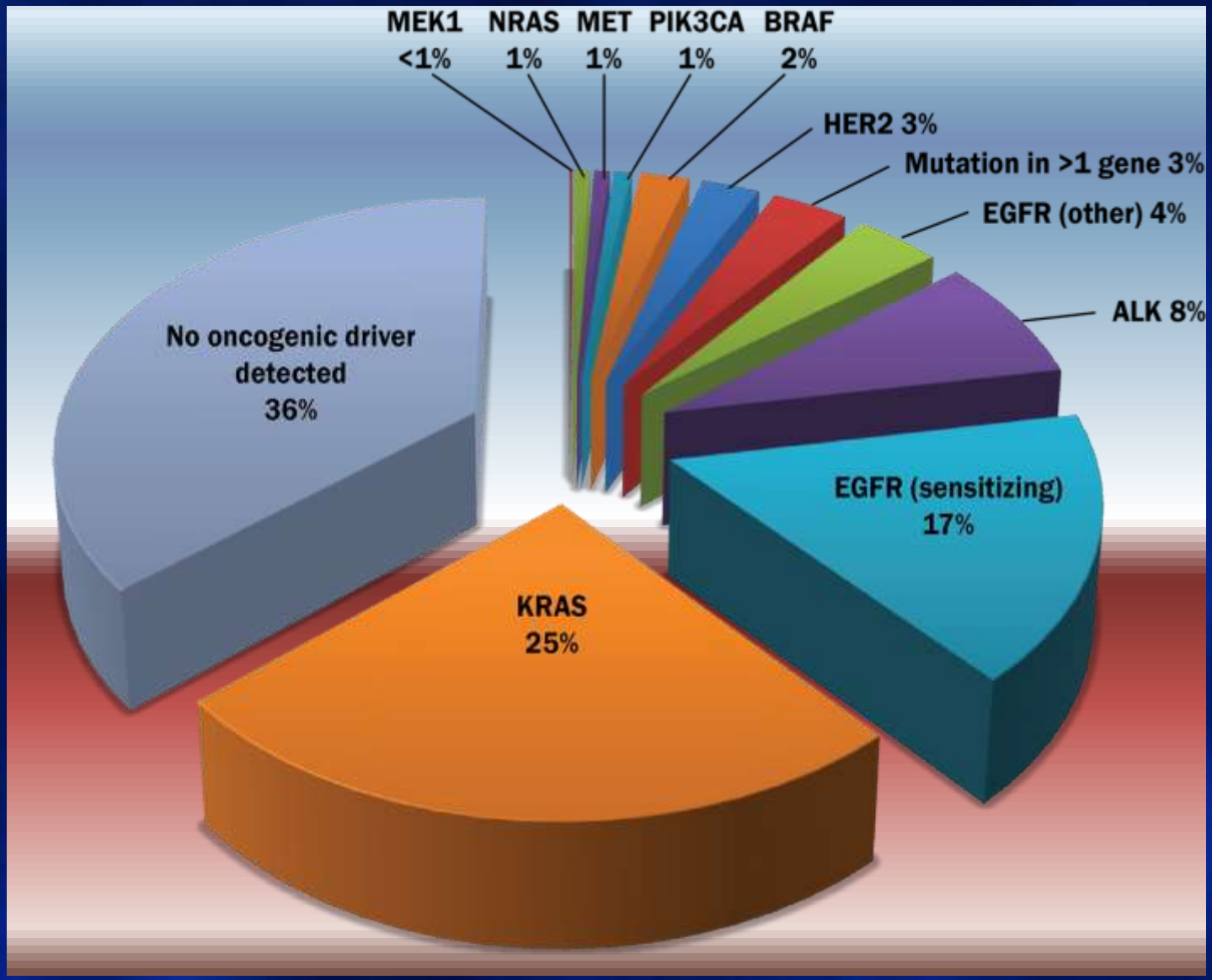
- MultiKinase Inhibitor of RET
  - VEGFR-2
  - EGFR
- Carbozantinib: Blocks multiple RTK including RET
- Approved for medullary thyroid cancer, and some preliminary activity in Lung ACA with RET

# Lung Cancer Mutation Consortium in Lung Adenocarcinoma

- 1007 patients tested for mutation
  - 733 tested for all 10 genes
  - 60% female; median age 63
  - 34% NS;58% former smokers
- Driver mutation found in 62%
  - Two mutations in 4%

J Clin Oncol 2013; 31: abst 8019

# Lung Cancer Mutation Consortium: Incidence of Drive Mutations



# Lung Cancer Mutation Consortium in Lung Adenocarcinoma

- 938 had follow-up data
  - 264 with driver mutation and Rx with a targeted agent: MST 3.5 yrs
  - 313 driver mutation and no Rx with targeted agent: MST 2.4 yrs
  - 361 with no driver mutation had a MST of 2.1 years

J Clin Oncol 2013; 31: abst 8019

# French Nationwide Screening for Six Driver Mutations

- EGFR, ALK, HER2, KRAS, BRAF, PI3KCA
- First 10,000 reported after one year
  - 63% males; 83% (ex)smokers
  - 76% adenoca
- 27% KRAS; 9% EGFR; 4% ALK
  - 1% HER2; 1.6% BRAF
- Feasibility of nationwide mutational testing

J Clin Oncol 2013; 31: abst 8000

# Dabrafenib Receives Breakthrough Status by FDA for BRAF Mutated LC

- Has clinical activity in BRAF V600E melanoma patients
  - Nearly 3000 LC patients per year USA
- 17 patients with this mutation treated 150 mg PO BID
  - Median age 69; 12/17 males; all ACA and 13 were former smokers
- 7 PRs of 13 (54%) evaluable: DuR was 6+,24+, 29 and 49 weeks

Planchard et al J Clin Oncol 2013; 31: abstr 8009

# HER2 Mutations in Lung Cancer

- HER2 insertions in exon 20 identified in 65 (1.7%) of 3,800 tested
  - Median age 60; 69% women; 52% NS; all ACA
- 16 patients Rx; 11 PRs
  - DCR of 93%  (n=15) with transtuzumab based Rx
  - DCR of 100% in 3 Rx with afatinib

Mazieres et al  J Clin Oncol 2013; 31:1997

# Genomic Characterization of Squamous Cell Lung Cancer

- **Comprehensive Genomic Characterization of Squamous Cell Lung Cancer: TCGA**

  *Nature 2012; 489:519-525*

- **Integrative and Comparative Genomic Analysis of Lung Squamous Carcinomas in East Asian Patients**

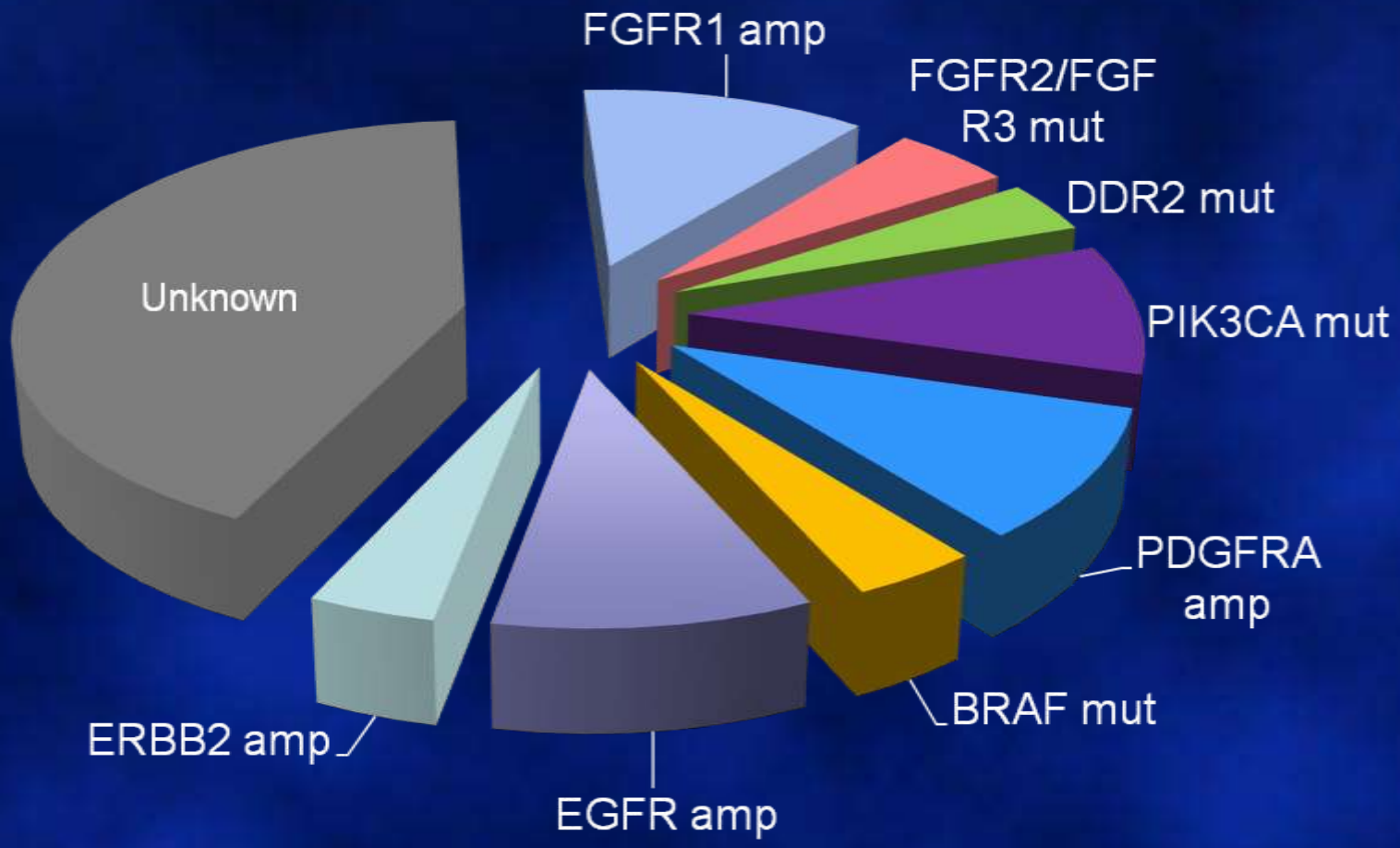
  Kim et al. *J Clin Oncol* 2013; 32:121-128

# Significantly Mutated Genes in Squamous Cell Lung Cancer

| | |
|---|---|
| TP53 | 81% |
| CCKN2A | 15% |
| PIK3CA | 16% |
| MLL2 | 20% |
| NFE2L2 | 15% |
| KEAP1 | 12% |
| PTEN | 8% |
| NOTCH1 | 8% |
| RB1 | 7% |

*TCGA Nature* 2012;489:519

# Genomic Characterization of Squamous Cell Lung Cancers: Potentially Targetable/Actionable Alterations



# TCGA: Squamous Cell

- Previously Unreported Mutation were Loss-of-Function in HLA-A Class I Major Histocompatability Gene
- Significantly Altered Pathways*
  - NFE2L2 and KEAP1 in 34% (oxidative stress response)
  - SOX2, TP63, NOTCH1 and 2 (squamous differentiation)

(Somatic mutations, copy number alterations, or up or down regulation)
*Nature* 2012;489:519

# Squamous Cell Carcinoma: Korean Study

- Seven Most Common Genes Mutated
  - TP53, RB1, PTEN, NFE2L2, KEAP1, MLL2, and PIK3CA
- Mutations Were Similar to TCGA
- Identified Recurrent Occurrence of FGFR3-TACC3 Fusion
  - Potentially actionable

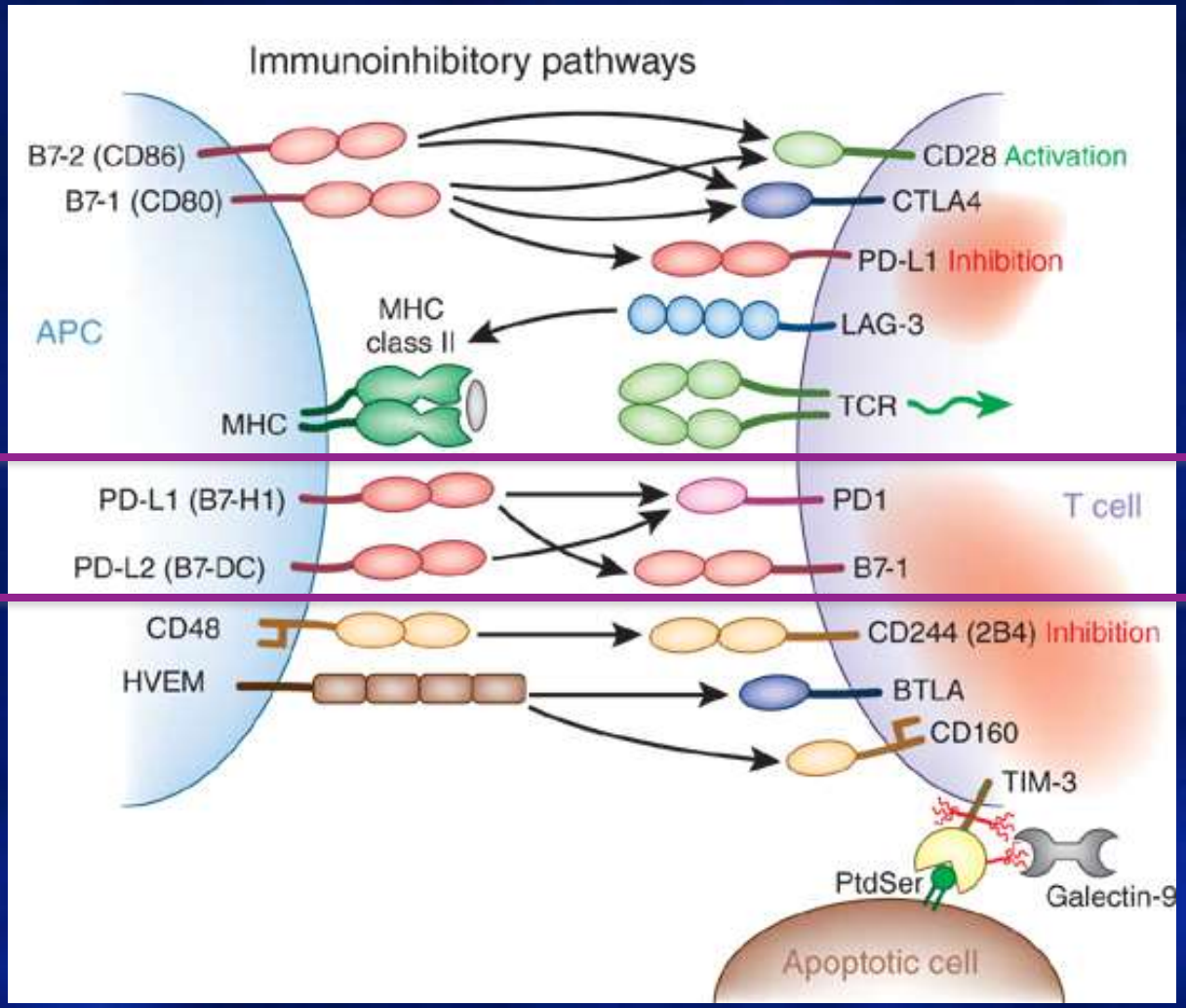
Kim et al. *J Clin Oncol* 2013;32:121-128

# FGFR Gene Fusions in Diverse Cancers

- Whole exome sequencing (DNA) and transcriptome sequencing (RNA)
- Various cancers tested for FGFR fusions
  - Present in many cancers including Squamous cell LC and HNSCC
  - Six lung cancer with fusions of FGFR1 (1), FGFR2 (1), FGFR3 (4)
- FGFR fusions are active kinases

Wu et al Cancer Discovery 2013; 3:636-47

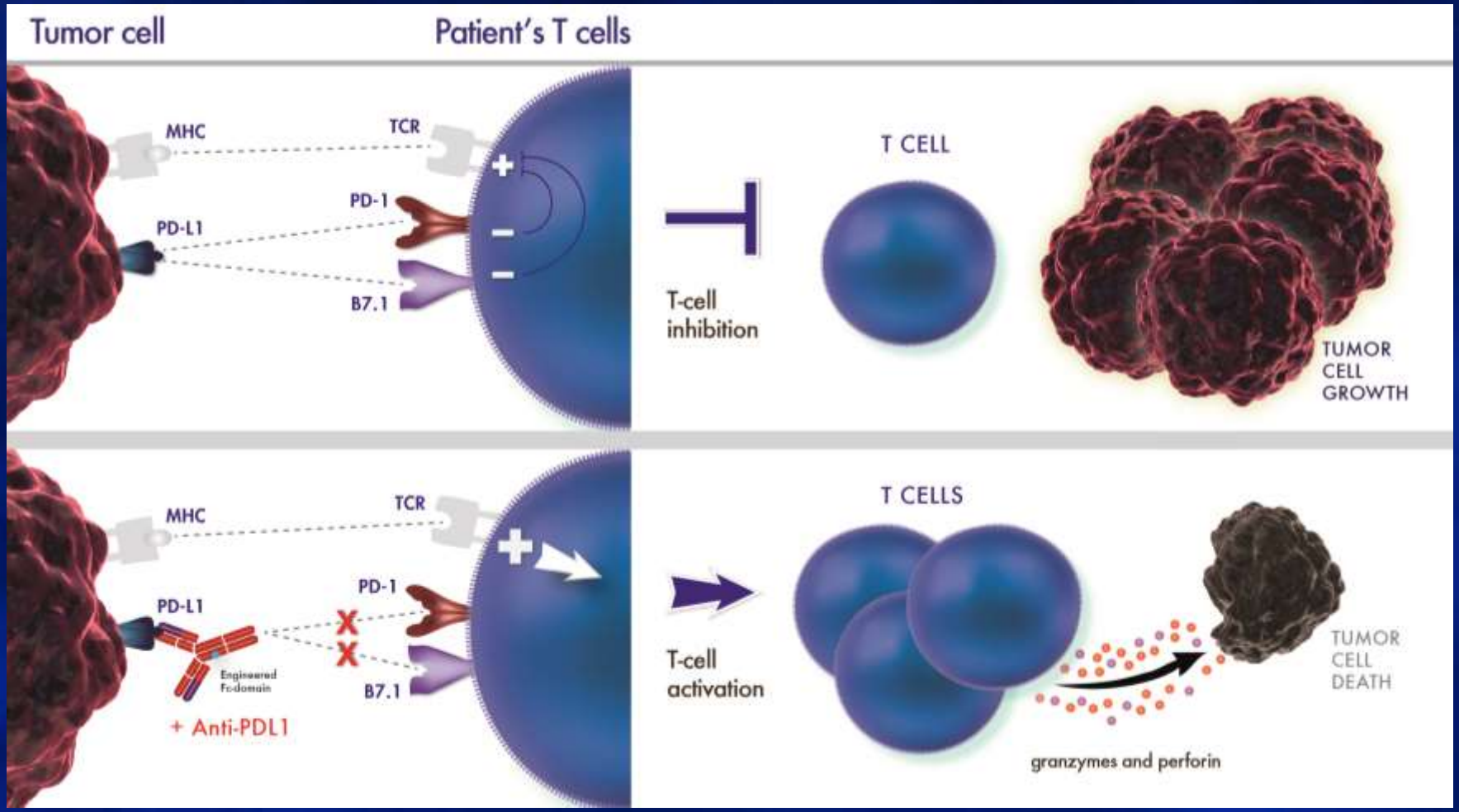
# How Do PD-L1 Blockade and PD-1 Blockade Differ?




Freeman & Sharpe, *Nat Immun* 2012; 13 (113)

Presented by: Natasha Leighl at ASCO Annual 13 Meeting

# MPDL3280A (Anti-PDL1) Inhibits the Binding of PD-L1 to PD-1 and B7.1




**Blocking PD-L1 restores T-cell activity, resulting in tumor regression in preclinical model. Binding to PD-L1 leaves PD-1/PD-L2 interaction intact and may enhance efficacy and safety.**

# Preliminary Efficacy Data in NSCLC

| Target | Agent | N | ORR% | SD>24 wks | 24 wk PFSR |
|---|---|---|---|---|---|
| PD-1 | Nivolumab-BMS-936558 1-10 mg/kg | 129 | 17.1% | 10.1% | -- |
| | Nivolumab 5,10 mg/kg + Platinum Doublet | 56 | ~45% | -- | 36-71% |
| | Lambrolizumab MK-3475 | 5 | 1/5 | -- | -- |
| PD-L1 | BMS-936559 1-10 mg/kg | 49 | 10% | 12% | 31% |
| | MPDL-3280A | 41 | 22% | 12% | 46% |

Brahmer et al. ASCO 2013 #8030; Rizvi et al. ASCO 2013, #8072; Brahmer et al NEJM 2012; Spigel et al. ASCO 2013 #8008

# www.MYCANCERGENOME.ORG

- Select a disease
- Select a gene
- Select a mutation

Vanderbilt-Ingram Cancer Center

National Jewish Health

# NCI Supported Genomic Clinical Trials

- SWOG 1400
  - Biomarker Driven master Protocol for Second Line Treatment of Lung cancer (4-6 arms)
- ALCHEMIST
  - Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial

# ALCHEMIST TRIAL

- Resected non-squamous Stage IB,II,III

  EGFR and ALK in CLIA Lab

  - Rest of tissue sent for testing in The Cancer Genome Atlas study
  - EGFR mutations enrolled in Alliance A081105 adjuvant erlotinib (n=410)
  - ALK fusions enrolled in E4512 adjuvant crizotinib (n=360)

# SWOG 1400

- Second line squamous cell mutational testing platform
- PI3K (PIK3CA mut): GDC0032 or chemo
- CDK4/6: PD0332991 or chemo
  - Mut CCND1,CDK4/6 amp,CDKN2 mut
- FGFR (amp,fus,mut): AZD4547 or chemo
- HGF (mut MET or amp):AMG102+erlotinib or chemo
- If no match then consider antiPDL1 vs CT

# Suggested Mutations Approach in 2014

**EGFR**

**ALK**

**KRAS**

# Additional FISH Testing 2014

ROS

RET

MET amp


WARNING:
SMOKING CAUSES
92% OF ORAL CANCERS
QUIT: 1800-438-2000
PM
Marlboro