# Diagnosis and Treatment of Adenocarcinomas and Squamous Cell Carcinomas of the Lung

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Stanford Cancer Center

# Learning Objectives

1. Discuss the range of genetic variants in non-small cell lung cancer (NSCLC) and how they are used to select targeted agents for patients with NSCLC
2. Identify current diagnosis and treatment paradigms for patients with squamous cell NSCLC
3. Identify and manage adverse events that occur with the use of immunotherapies across all subtypes of NSCLC

# Financial Disclosure

- Dr. Das has nothing to disclose.
- Ms. Holmes Tisch has nothing to disclose.

# Outline

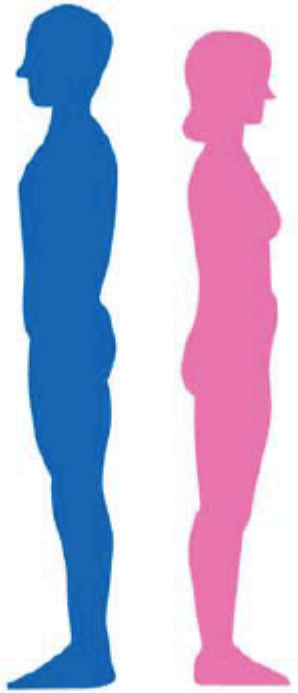
- NSCLC: Staging and diagnosis
- Treatment based upon histology
- Targeted agents
- Immunotherapy in NSCLC

EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase.

# NSCLC: Staging and Diagnosis

# Annual Cancer Incidence: US

**Estimated New Cases**

| Males | | | | Females | | |
|---|---|---|---|---|---|---|
| Prostate | 220,800 | 26% |  | Breast | 231,840 | 29% |
| Lung & bronchus | 115,610 | 14% | | Lung & bronchus | 105,590 | 13% |
| Colon & rectum | 69,090 | 8% | | Colon & rectum | 63,610 | 8% |
| Urinary bladder | 56,320 | 7% | | Uterine corpus | 54,870 | 7% |
| Melanoma of the skin | 42,670 | 5% | | Thyroid | 47,230 | 6% |
| Non-Hodgkin lymphoma | 39,850 | 5% | | Non-Hodgkin lymphoma | 32,000 | 4% |
| Kidney & renal pelvis | 38,270 | 5% | | Melanoma of the skin | 31,200 | 4% |
| Oral cavity & pharynx | 32,670 | 4% | | Pancreas | 24,120 | 3% |
| Leukemia | 30,900 | 4% | | Leukemia | 23,370 | 3% |
| Liver & intrahepatic bile duct | 25,510 | 3% | | Kidney & renal pelvis | 23,290 | 3% |
| **All Sites** | **848,200** | **100%** | | **All Sites** | **810,170** | **100%** |

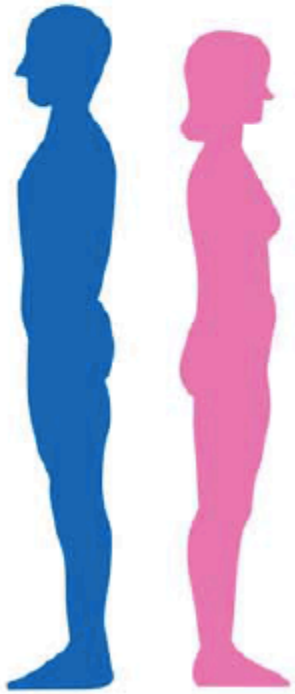
Siegel RL, et al. *CA Cancer J Clin* 2015;65:5-29.

# Annual Cancer Deaths: US

**Lung and bronchus cancer account for more deaths than breast, colon, and prostate cancer combined**

**Estimated Deaths**

| Males | | | Females | | |
|---|---|---|---|---|---|
| Lung & bronchus | 86,380 | 28% | Lung & bronchus | 71,660 | 26% |
| Prostate | 27,540 | 9% | Breast | 40,290 | 15% |
| Colon & rectum | 26,100 | 8% | Colon & rectum | 23,600 | 9% |
| Pancreas | 20,710 | 7% | Pancreas | 19,850 | 7% |
| Liver & intrahepatic bile duct | 17,030 | 5% | Ovary | 14,180 | 5% |
| Leukemia | 14,210 | 5% | Leukemia | 10,240 | 4% |
| Esophagus | 12,600 | 4% | Uterine corpus | 10,170 | 4% |
| Urinary bladder | 11,510 | 4% | Non-Hodgkin lymphoma | 8,310 | 3% |
| Non-Hodgkin lymphoma | 11,480 | 4% | Liver & intrahepatic bile duct | 7,520 | 3% |
| Kidney & renal pelvis | 9,070 | 3% | Brain & other nervous system | 6,380 | 2% |
| **All Sites** | **312,150** | **100%** | **All Sites** | **277,280** | **100%** |



Siegel RL, et al. *CA Cancer J Clin* 2015;65:5-29.

# Presenting Symptoms of Lung Cancer

- Local symptoms
  - Cough, dyspnea, hemoptysis, chest pain
- General symptoms
  - Fatigue, weight loss
- Symptoms secondary to distant metastases
  - Bone pain, neurologic symptoms
- Paraneoplastic syndromes
  - SIADH

SIADH = syndrome of inappropriate antidiuretic hormone secretion.

# Workup for Lung Cancer: Tissue Is Key

History/Physical exam

Chest x-ray, routine labs

Chest CT (include adrenals)

Bronchoscopy, CT-guided biopsy, thoracentesis

CT = computed tomography.

# NSCLC: AJCC/IASLC Staging

| Lung Cancer Staging: Differences Between the AJCC Cancer Staging Manual, 6th and 7th Editions | | |
|---|---|---|
| | **AJCC 6th Edition** | **AJCC 7th Edition** |
| T descriptor | | |
| T1 | ≤ 3 cm | *T1a: ≤ 2 cm*<br>*T1b: > 2 cm but ≤ 3 cm* |
| T2 | 3 cm or:<br>Invades visceral pleura<br>Atelectasis of less than entire lung<br>Proximal extent at least 2 cm from carina | *T2a: > 3 cm but ≤ 5 cm*<br>*T2b: > 5 cm but ≤ 7 cm*<br>Or tumors ≤ 7 cm with invasion of visceral pleura, atelectasis of less than entire lung, proximal extent at least 2 cm from carina |
| T3 | Tumors with invasion of chest wall, diaphragm, mediastinal pleura | Tumors > 7 cm or with:<br>Direct invasion of chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, main bronchus < 2 cm from carina (without involvement of carina)<br>*Tumor nodules in same lobe as primary tumor* |
| T4 | Tumor of any size with:<br>Invasion of mediastinum, heart, great vessels, trachea, esophagus<br>*Malignant pleural or pericardial effusions*<br>*Tumor nodules in the same lobe as the primary* | Tumor of any size with:<br>Invasion of mediastinum, heart, great vessels, trachea, esophagus<br>*Metastatic tumor nodules in different lobe from primary tumor* |
| N descriptor | | No changes |
| M descriptor | | |
| M1 | Distant metastasis: *metastatic tumor nodules in a different lobe from the primary tumor* | Subdivided into:<br>**M1a**: *Malignant pleural or pericardial effusion* pleural nodules, nodules in contralateral lung<br>**M1b**: Distant metastasis |

AJCC/IASLC = American Joint Committee on Cancer/International Association for the Study of Lung Cancer.

Edge SB, et al. *AJCC Cancer Staging Manual*, 7th edition. 2010. p. 253-70.

# Biopsy: Establish Diagnosis, Determine Histologic Subtype, Conduct Molecular Testing

- Need to ensure adequate tissue is obtained for histologic subtyping and molecular analysis (avoid bone biopsies)
- Histologic subtyping
  - Nonsquamous vs. squamous histology
- Determination of EGFR mutation and ALK/ROS translocations is indicated in all *nonsquamous* histologies
  - Should other genes be evaluated? (e.g., KRAS, BRAF, HER2, RET)
  - Should squamous histology be tested?
- Re-biopsy at the time of disease progression
  - Helps in determining resistance in EGFR-mutated and ALK+ cases
- Liquid biopsies (cell-free DNA) are increasingly being used

# Pathology of Lung Cancer: Overview

- Major histologic classifications
  - Small cell lung cancer (10%–15%)
  - NSCLC (85%–90%)
    - Adenocarcinoma (30%–40%)
    - SCC (20%–25%)
    - Large cell carcinoma (10%–15%)
    - Other, mixed (3%–5%)

SCC = squamous cell carcinoma.

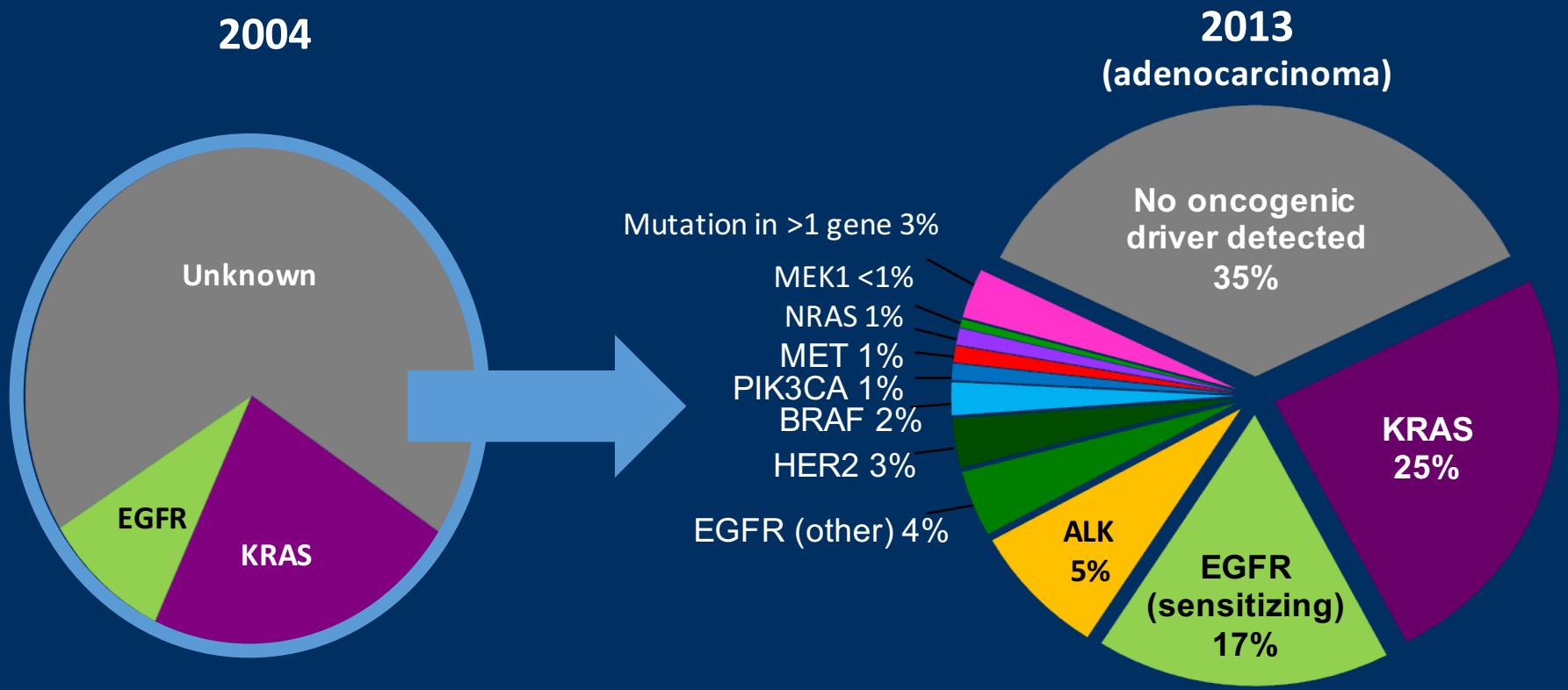
American Cancer Society. Lung cancer (non-small cell). http://www.cancer.org/acs/groups/cid/documents/webcontent/003115-pdf.pdf

# Adenocarcinoma vs. Squamous

| | Adenocarcinoma | Squamous |
|---|---|---|
| % NSCLC | 30%–40% | 25%–30% |
| Age | Bimodal with younger subset | Older |
| Male/Female | Female | Male |
| Location | Peripheral | Central |
| Smoking | Never smoker subset | Usually smoking related |
| Therapies contraindicated | No | Pemetrexed, bevacizumab |
| Biomarker-driven targeted therapy | Yes | No |
| Improved survival | Yes | No |

Li T, et al. *J Clin Oncol* 2013;31:1039-49.

# Evolving Molecular Classification of NSCLC Over the Past Decade




Pao W, et al. *Lancet Oncol* 2011;12:175-80; Blakely CM, et al. *Cancer Discov* 2012;2:872-5.

# Treatment Options in NSCLC

- Chemotherapy
  - Histologic subtyping
- Targeted therapy
  - EGFR
  - ALK
  - ROS1
- Checkpoint inhibitors
  - Anti-PD-1
  - Anti-PD-L-1
  - Anti-CTLA-4

# Considerations for First-Line Therapy for Advanced NSCLC

- Clinical features
  - Performance status
  - Smoking cessation counseling
  - CNS metastases
  - Prior chemotherapy in the locally advanced or adjuvant setting and time to recurrence
- Histology
  - Adenocarcinoma vs. squamous vs. large cell neuroendocrine
- Molecular testing
  - EGFR
  - ALK
  - ROS
  - Next-generation sequencing

CNS = central nervous system.

# Guidelines for Molecular Testing in NSCLC

- Adenocarcinoma/large cell/NSCLC NOS
  - EGFR
  - ALK
  - Test for EGFR and ALK as part of broader molecular profiling
  - ROS when EGFR/ALK are negative or unknown
- Squamous cell
  - Consider EGFR and ALK testing in certain patients
    - Never-smokers
    - Mixed histology

| Pack-years | *EGFR* mutation (%) | 95% CI |
|---|---|---|
| Never | 52 | 48–56 |
| 1–5 | 34 | 25–43 |
| 6–10 | 34 | 26–44 |
| 11–15 | 18 | 11–26 |
| 16–25 | 11 | 7–16 |
| 26–50 | 8 | 6–11 |
| 51–75 | 9 | 5–13 |
| >75 | 4 | 2–8 |

CI = confidence interval; NOS = not otherwise specified.

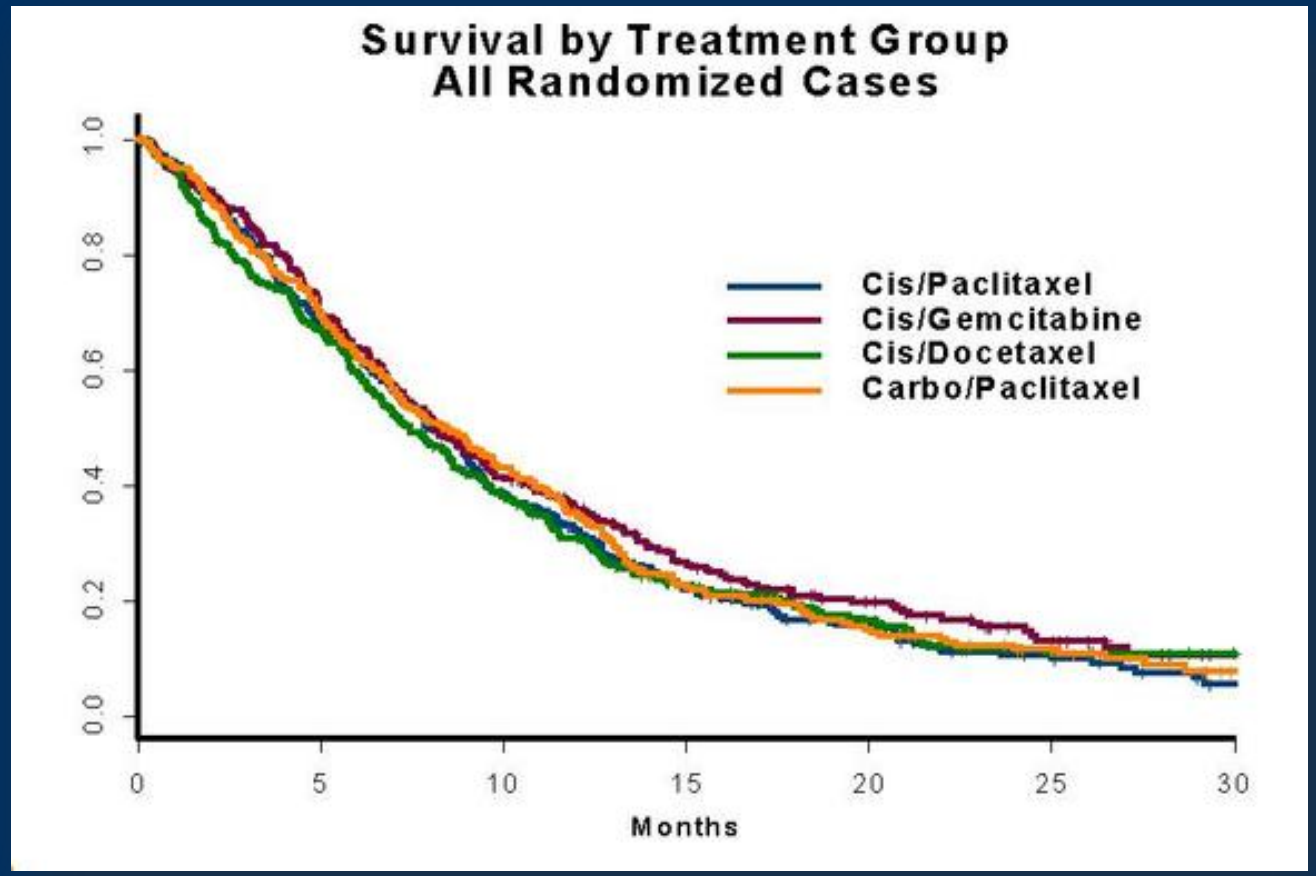
National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Non-Small-Cell Lung Cancer. v4.2016; D'Angelo SP, et al. *J Clin Oncol* 2011;29:2066-70.

# Treatment Based Upon Histology

# First-Line Stage IV NSCLC Treatment

- A combination of two chemotherapy drugs is standard (platinum-based)
- New strategies are under development to help us tailor therapy
- Standard is four cycles (~3 months)
- Second-line therapy can start either immediately (maintenance) or at progression

# ECOG 1594: Overall Survival by Treatment Group

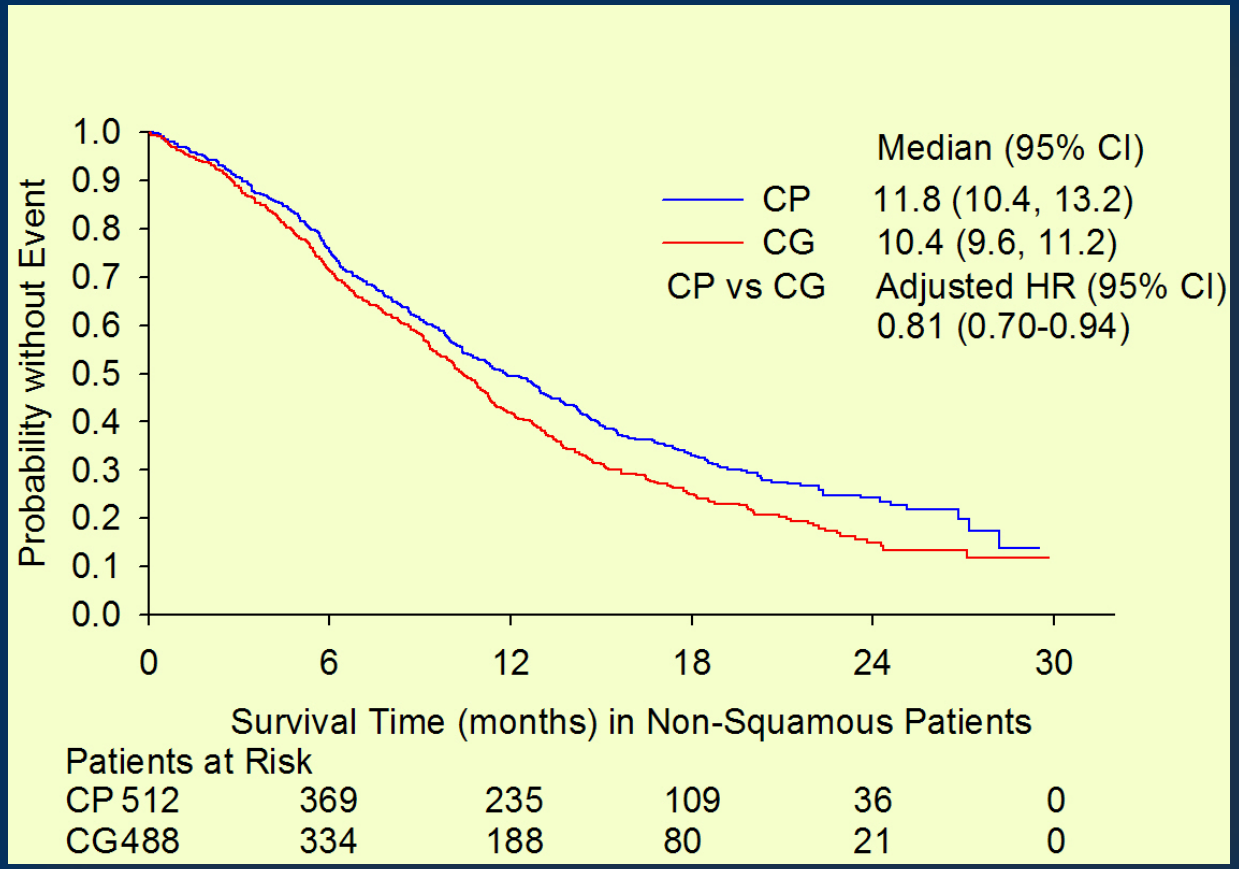



Schiller J, et al. *N Engl J Med* 2002;346:92-8.

# Histology Matters: Cisplatin/Pemetrexed vs. Cisplatin/Gemcitabine

Phase III, advanced-stage, previously untreated NSCLC

- Cisplatin/gemcitabine (CG)
- Cisplatin/pemetrexed (CP)



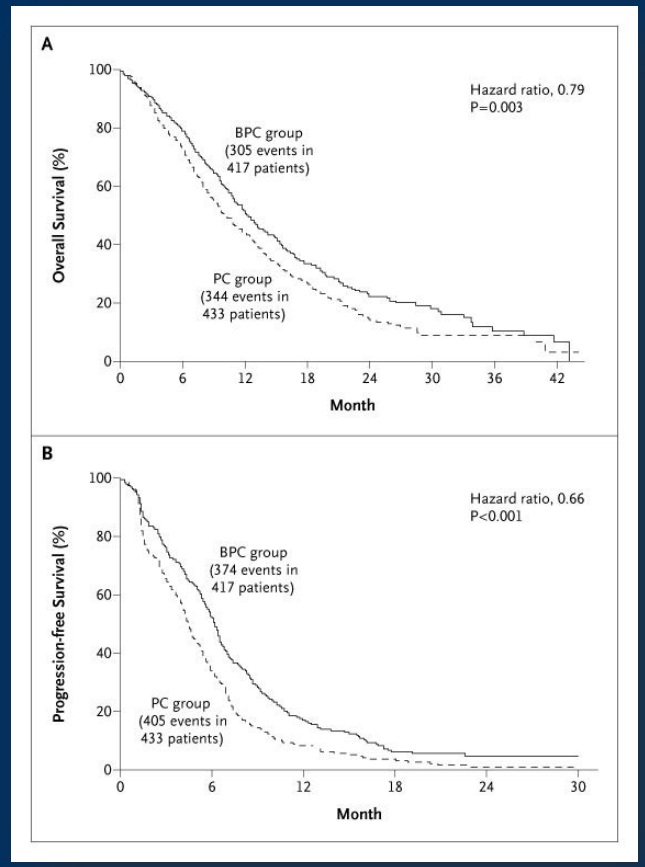

HR = hazard ratio.

Scagliotti GV, et al. *J Clin Oncol* 2008;2:3543-51..

# ECOG 4599: Carboplatin/Paclitaxel +/- Bevacizumab in Nonsquamous NSCLC

Phase III, recurrent or advanced nonsquamous NSCLC, no prior chemotherapy (N = 878)

- Carboplatin/paclitaxel (CP)
- Carboplatin/paclitaxel/ bevacizumab* (CP+ B)




*Bevacizumab is a monoclonal antibody that targets VEGF
VEGF = vascular endothelial growth factor.

Sandler A, et al. *N Engl J Med* 2006;355:2542-50.

# Nab-paclitaxel in NSCLC

Phase III, stage IIIb/IV NSCLC, ECOG PS 0-1, no prior chemotherapy (N = 1,052)

Carboplatin Paclitaxel (PC)

Carboplatin Nab-paclitaxel (nPC)

Overall study population

| Endpoint | PC (n = 531) | nPC (n = 521) | Significance |
|---|---|---|---|
| ORR | 25 | 33 | *P* < .005 |
| PFS (mo) | 5.8 | 6.3 | HR: 0.902; *P* < .214 |
| OS (mo) | 11.2 | 12.1 | HR: 0.922; *P* = .271 |

Squamous cell subset

| Endpoint | PC (n = 531) | nPC (n = 521) | Significance |
|---|---|---|---|
| ORR | 41 | 24 | *P* < .001 |

ECOG PS = Eastern Cooperative Oncology Group performance status; PFS = progression-free survival; ORR = overall response rate; OS = overall survival.

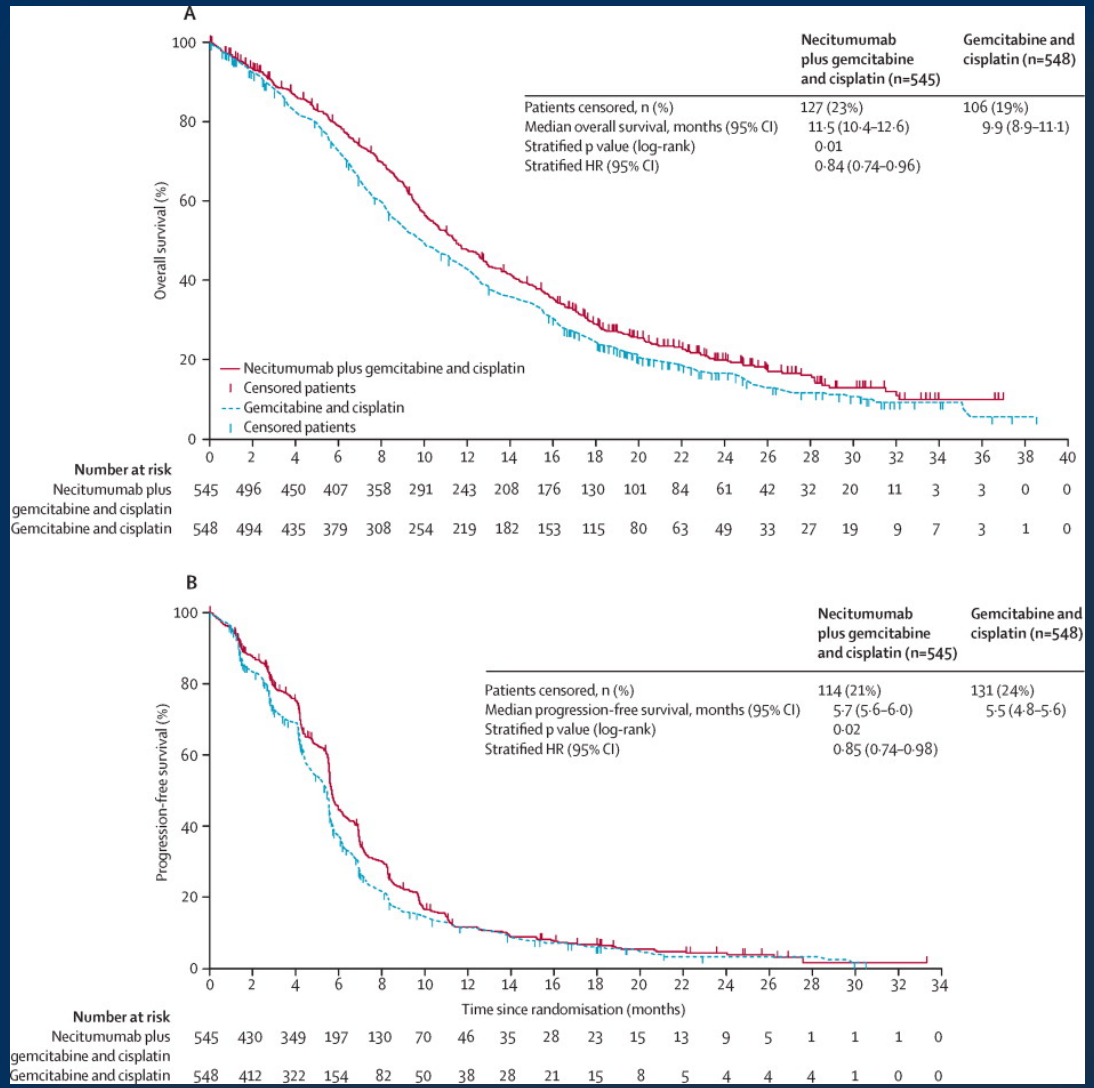
Socinski MA, et al. *J Clin Oncol* 2012;30:2055-62.

# SQUIRE: Necitumumab in Squamous Lung Cancer

Phase III, stage IV squamous NSCLC, no prior chemo, ECOG PS 0-2 (N = 1,093)

Gemcitabine/ cisplatin

Necitumumab*/ gemcitabine/ cisplatin




*Necitumumab is a second-gen EGFR antibody

Thatcher N, et al. *Lancet Oncol* 2015;16:763-74.

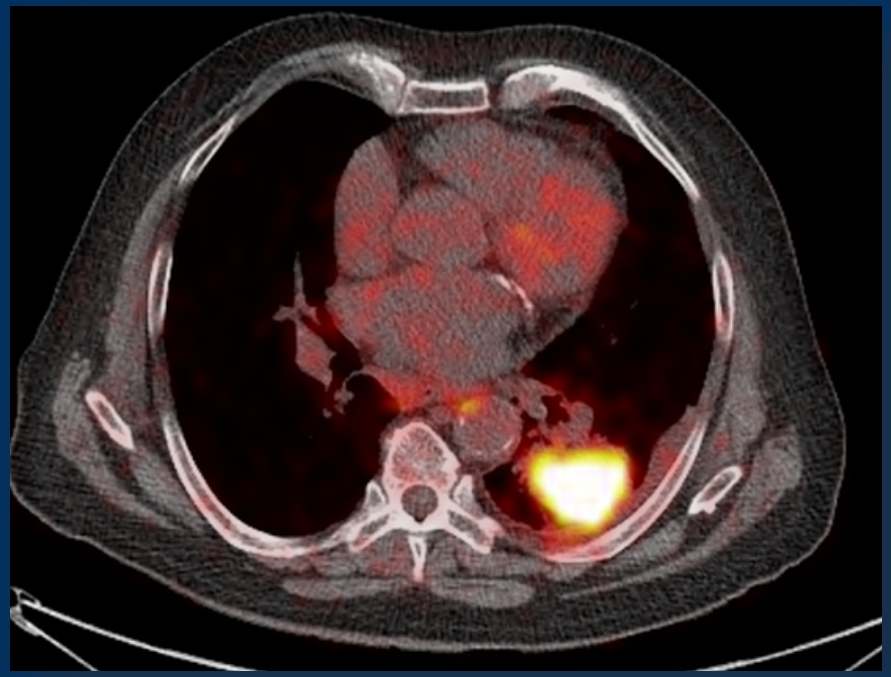
# Case 1: SCC Case

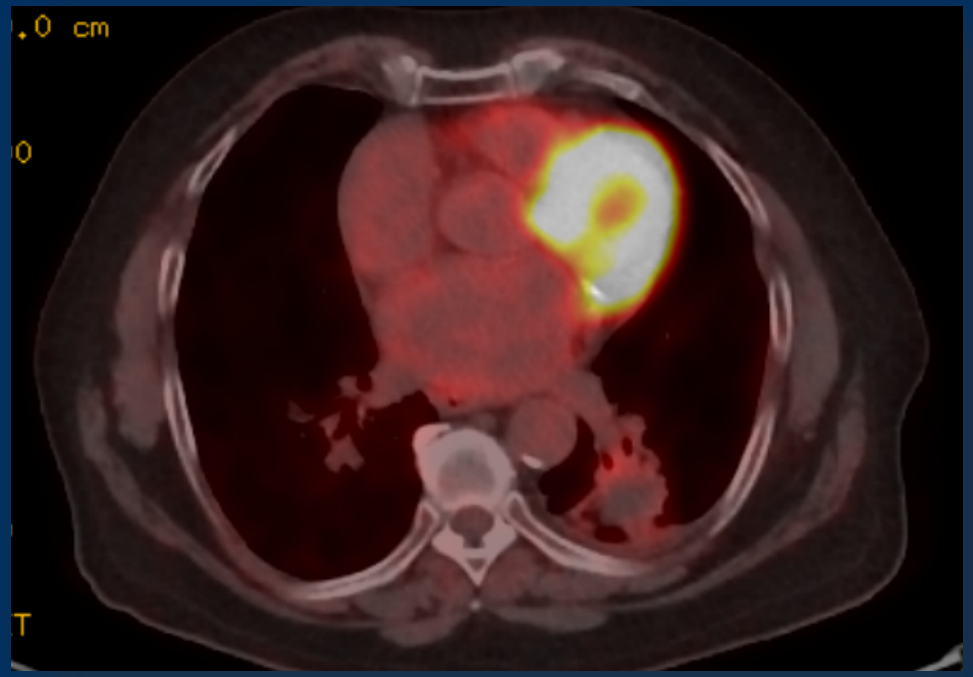
- Mr. K is an 80-year-old male who initially presented to PCP with cough x 4–5 months in August 2015
- Initial CT imaging showed 5 x 7-cm mass in LLL extending to chest wall with prominent mediastinal LNs and a 2 x 3-cm left adrenal mass
- CT-guided L lung biopsy showed squamous cell lung cancer, p63+, CK 5/6+, TTF1-
- Staging: T4N2M1b stage IV squamous cell lung cancer
- Initial therapy: Platinum doublet, carbo AUC 5, and paclitaxel 200 mg/m$^2$ every 3 weeks x 4 cycles

AUC = area under concentration-time curve; L lung = left lung; LLL = lower left lobe; LNs = lymph nodes; PCP = primary care physician; TTF1 = thyroid transcription factor 1.

# Case 1: Initial Response

- Scans at baseline (left) and after 4 cycles doublet (right)






Images courtesy of Stanford University.

# SCC Case: Disease Progression

- Progression in January 2016 in brain and body
- Treated with stereotactic radiosurgery to five new brain lesions
- Started nivolumab x four cycles with PD, gemcitabine x 3 cycles with PD, and then docetaxel x two cycles with PD
- Received palliative XRT to 3,000 cGy to LLL and rib
- Unfortunately, patient now has further progression in the brain and is proceeding with supportive care alone

PD = partial disease; XRT = radiation therapy.

# Maintenance Chemotherapy Options

| First-line therapy | | Treatment after first-line therapy | |
|---|---|---|---|
| **Platinum doublet x 4–6 cycles** | CR/PR/SD → | **Same drug(s) Options: bevacizumab, pemetrexed** | Continuation maintenance |
| **Platinum doublet x 4–6 cycles** | CR/PR/SD → | **Different drug(s) Options: pemetrexed, docetaxel, erlotinib** | Switch maintenance |
| **Platinum doublet x 4–6 cycles** | CR/PR/SD → | **Different drug(s)** | "Early" second-line therapy |
| **Platinum doublet x 4–6 cycles** | PD → | **Different drug(s)** | Second-line therapy |

SD = stable disease.

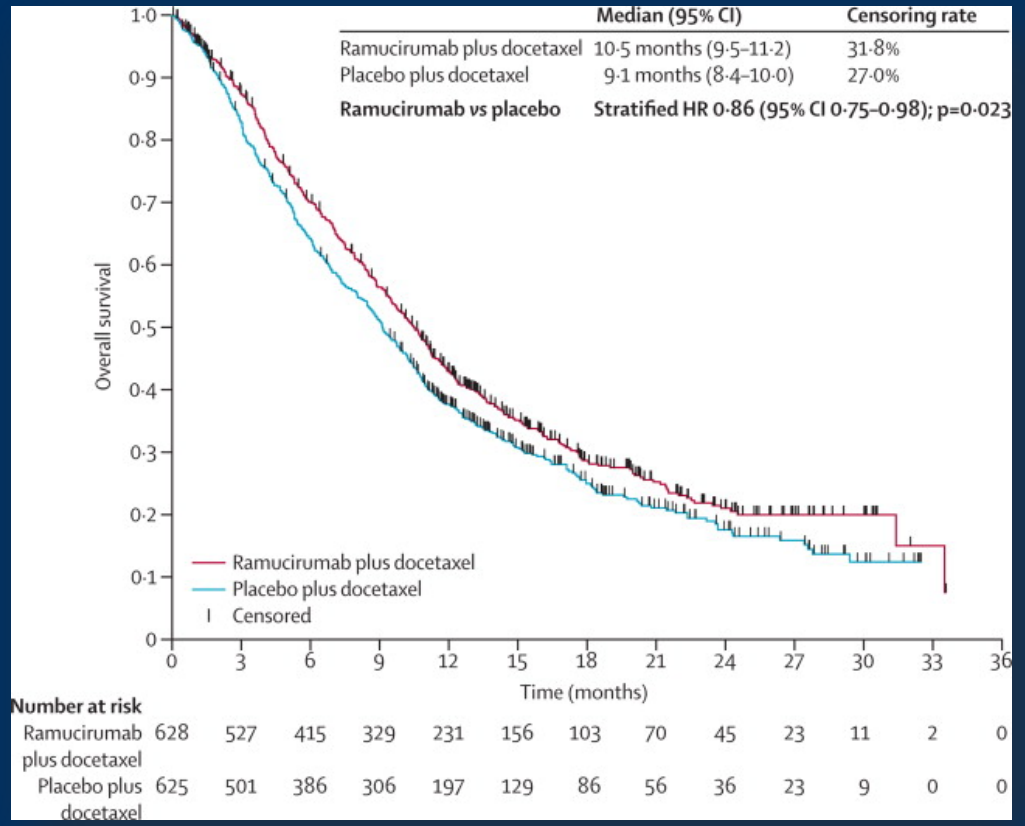
Adapted from Gandara DR, et al. *Clin Lung Cancer* 2012;13:321-5.

# REVEL: Ramucirumab in NSCLC

Phase III, stage IV NSCLC, progressed after first-line platinum chemo (N = 1,253)

Placebo + docetaxel

Ramucirumab* + docetaxel




*Ramucirumab is an IgG antibody targeting VEGFR-2.

IgG = immunoglobulin G; VEGR-2 = vascular endothelial growth factor receptor 2.

Garon EB, et al. *Lancet*. 2014;384:665-73.

# Targeted Agents

# *EGFR* Mutations: Background

- Found in 10%–15% of all NSCLC patients
- Predict responsiveness to EGFR TKIs (erlotinib, gefitinib, afatanib)
- More common in never-smokers, adenocarcinomas, females, Asian ethnicity
- Predominantly located in *EGFR* exons 18–21
  - 85% of *EGFR* mutations are either deletions in exon 19 or a single point mutation in exon 21 (L858R)
- The specific *EGFR* mutation identified is important
  - There are sensitive mutations, primary resistance mutations (often exon 20), and acquired resistance mutations (T790M)

TKIs = tyrosine kinase inhibitors.

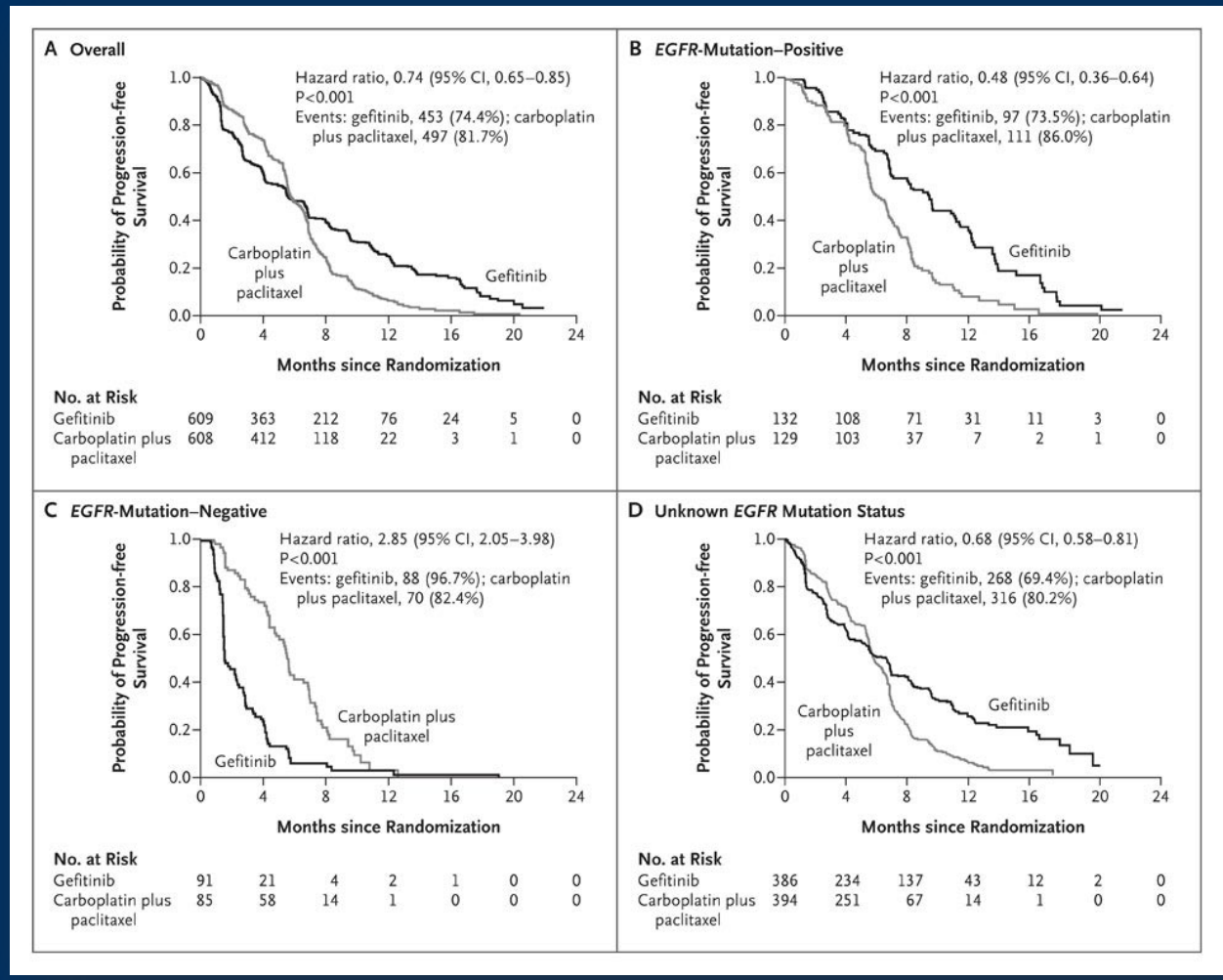
Pao W, et al. *J Clin Oncol* 2005;23:2556-68; Wu YL, et al. *J Thorac Oncol* 2007;2:430-9.

# IPASS: First-Line Gefitinib vs. Carbo/Paclitaxel

Phase III, previously untreated patients with stage IIIB/IV NSCLC, adenocarcinoma, never or extra-light smokers, WHO PS 0-2 (N = 1,217)

Gefitinib 250 mg po daily

Carboplatin + paclitaxel




*Gefitinib is an EGFR TKI

po = orally; WHO PS = World Health Organization performance status.

Mok TS, et al. *N Engl J Med* 2009;361:947-57.

# LL3 and LL6: First-line Afatanib vs. Chemo in Stage IV With *EGFR* mutation

| Median PFS (months) | Lux Lung-3[1] | Lux Lung-6[2] |
|---|---|---|
| Afatanib | 11.1 | 11.0 |
| Chemotherapy | 6.9 | 5.6 |
| HR | 0.58 (*P* = .001) | 0.28 (*P* < .001) |

| Median OS (months) in EGFR del (19) patients[3] | Lux Lung-3 | Lux Lung-6 |
|---|---|---|
| Afatanib | 33.3 | 31.4 |
| Chemotherapy | 21.1 | 18.4 |
| HR | 0.54 (*P* = .002) | 0.64 (*P* = .023) |

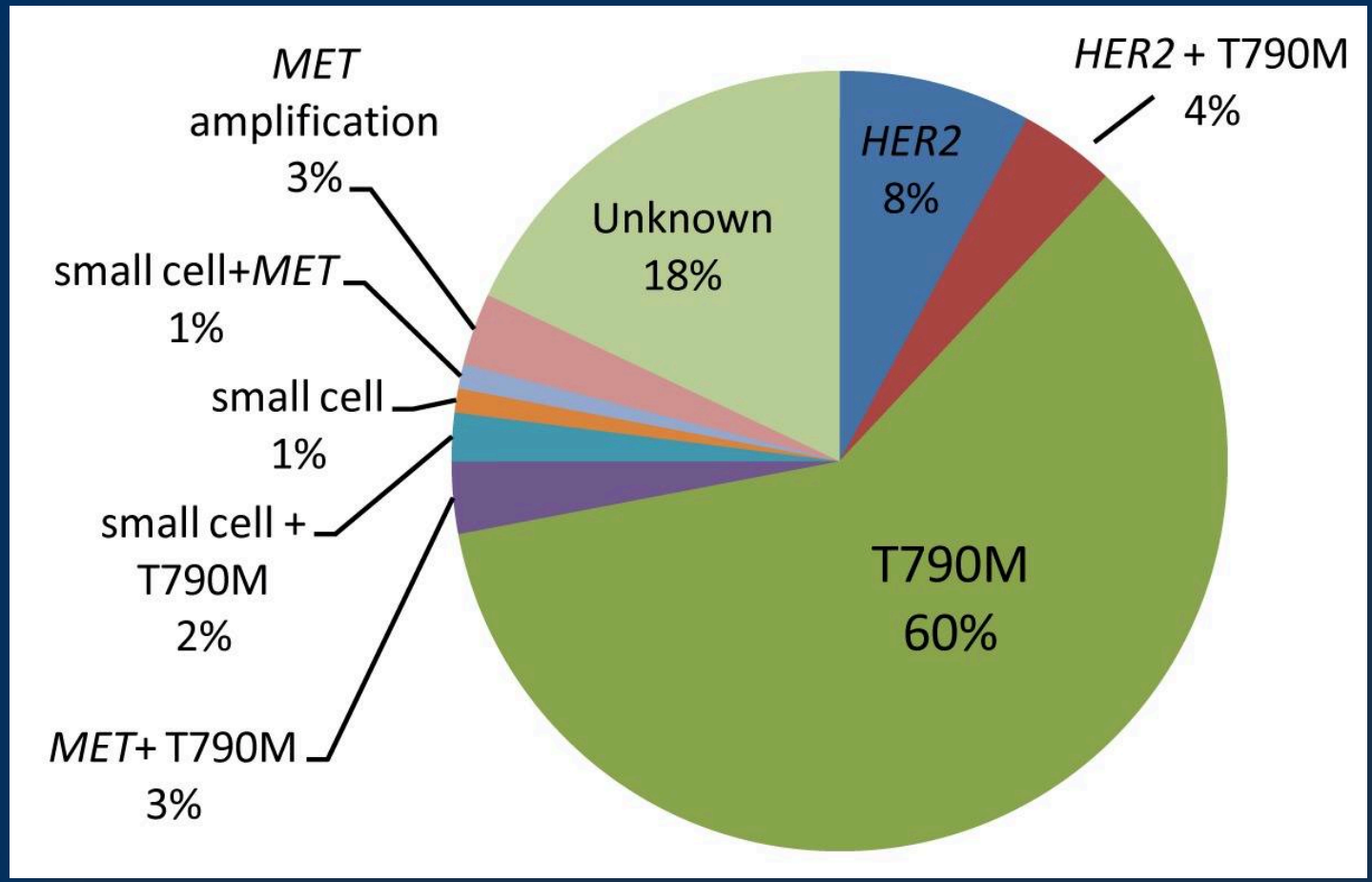
[1]Sequist L, et al. *J Clin Oncol*. 2013;31:3327-34; [2]Wu YL, et al. *Lancet Oncol*. 2014;15:213-22; [3]Sequist L, et al. Chicago Multidisciplinary Symposium in Thoracic Oncology 2014. Abstract 9.

# Toxicities of EGFR Inhibitors

- Most common toxicities are acneiform rash and diarrhea
- Mostly mild to moderate; requires therapeutic intervention in 30% of cases
- Proactive management may decrease severity and maximize treatment outcome
- Rash predicts responsiveness to treatment and is associated with longer PFS and OS

Melosky B, et al. *Curr Oncol* 2009;16:16-26; Lacouture ME, et al. *Oncology (Williston Park)* 2007;21(11 suppl 5):17-21; Liu HB, et al. *PLoS One* 2013;8:e55128.

# Disease Progression on an EGFR TKI



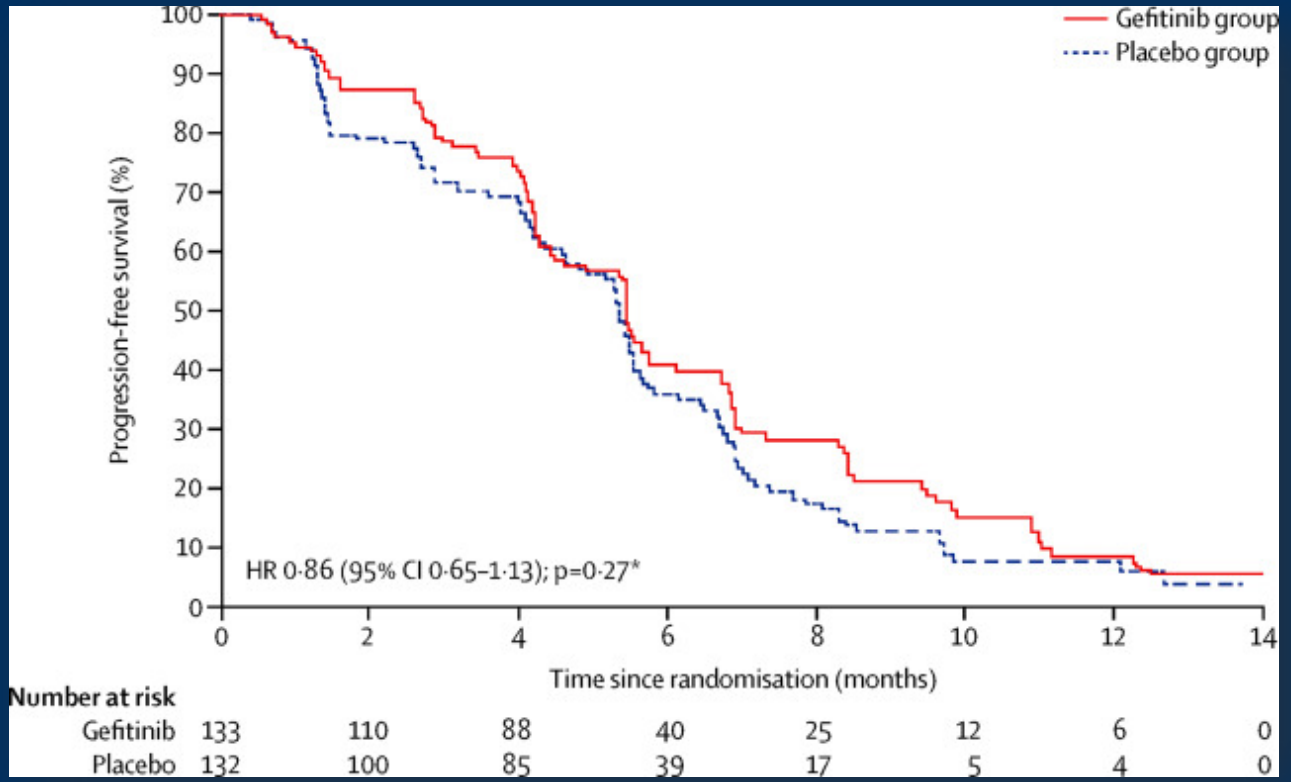

Yu H, et al. *Clin Cancer Res* 2013;19:2240-7.

# IMPRESS: Cis/Pem ± Gefitinib in Stage IIIb/IV NSCLC With *EGFR* Mutation

Phase III, stage IV *EGFR* mutation+, previous disease control with first-line gefitinib and recent disease progression (N = 265)

Pemetrexed/ Cisplatin + Placebo

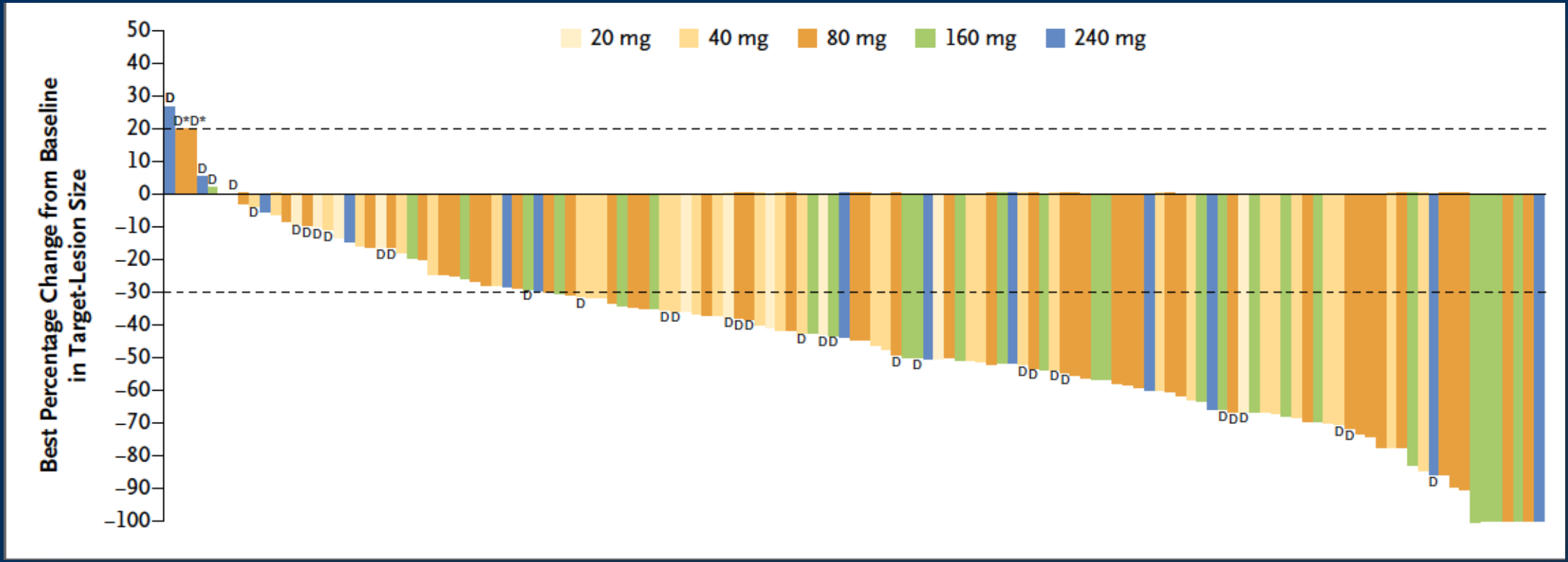
Pemetrexed/ Cisplatin + Gefitinib




Soria JC, et al. *Lancet Oncol* 2015;16:990-8.

# Osimertinib: Third-Generation EGFR TKI

**AZD9291/Osimertinib ORR**
- **EGFR T790M+ 61%**
- **EGFR T790M- 21%**




Janne PA, et al. *N Engl J Med* 2015;372:1689-99; Sequist LV, et al. *N Engl J Med* 2015;372:1700-9.

# Case 2: EGFR Mutant Case

- Mrs. G is a 46-year-old Asian woman who initially presented with worsening back pain in October 2013
- Found to have a left hilar mass, mediastinal LNs, multiple bone metastases, and a 2.3-cm left parietal metastasis
- Underwent bronchoscopy and L4 biopsy, which revealed adenocarcinoma, TTF-1+
- Craniotomy with left parietal mass resection; molecular testing revealed EGFR exon 19 deletion
- First-line therapy with erlotinib initially at 150 mg, but dose reduced to 100 mg daily due to intolerance of rash and diarrhea

# Case 2: Progression on Erlotinib

- December 2014: disease progression in the brain, started pulse dose erlotinib with poor tolerance
- Started carboplatin AUC 6, pemetrexed 500 mg/m$^2$, and bevacizumab 15 mg/kg x six cycles followed by seven cycles of maintenance pemetrexed and bevacizumab
- November 2015: PD in body and brain with question of LC
- Started investigational systemic therapy with good CNS penetration

LC = leptomeningeal carcinomatosis.

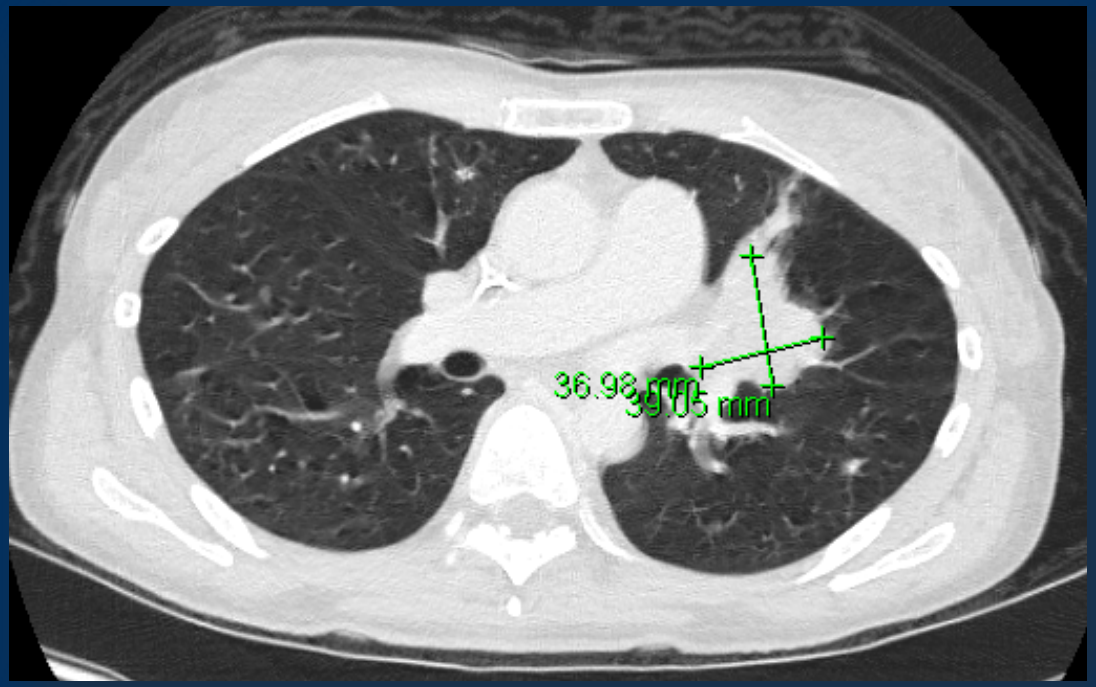
# Case 2: Third-Generation EGFR Inhibitors

- January 2016: PD with significant clinical decline in mental status, balance, nausea/vomiting and pain, more significant progression of LC
- Underwent blood biopsy for T790M, found to be negative
- Treated with WBRT and started osimertinib 80 mg daily

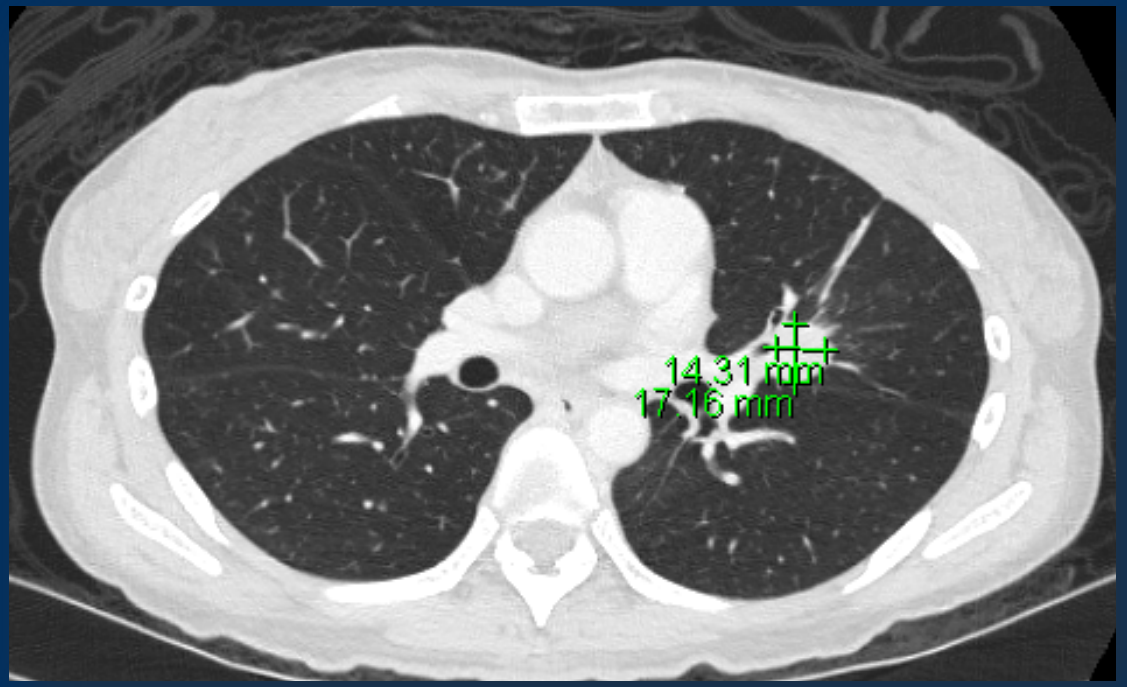
WBRT = whole-brain radiation therapy.

# Imaging on Osimertinib

Baseline

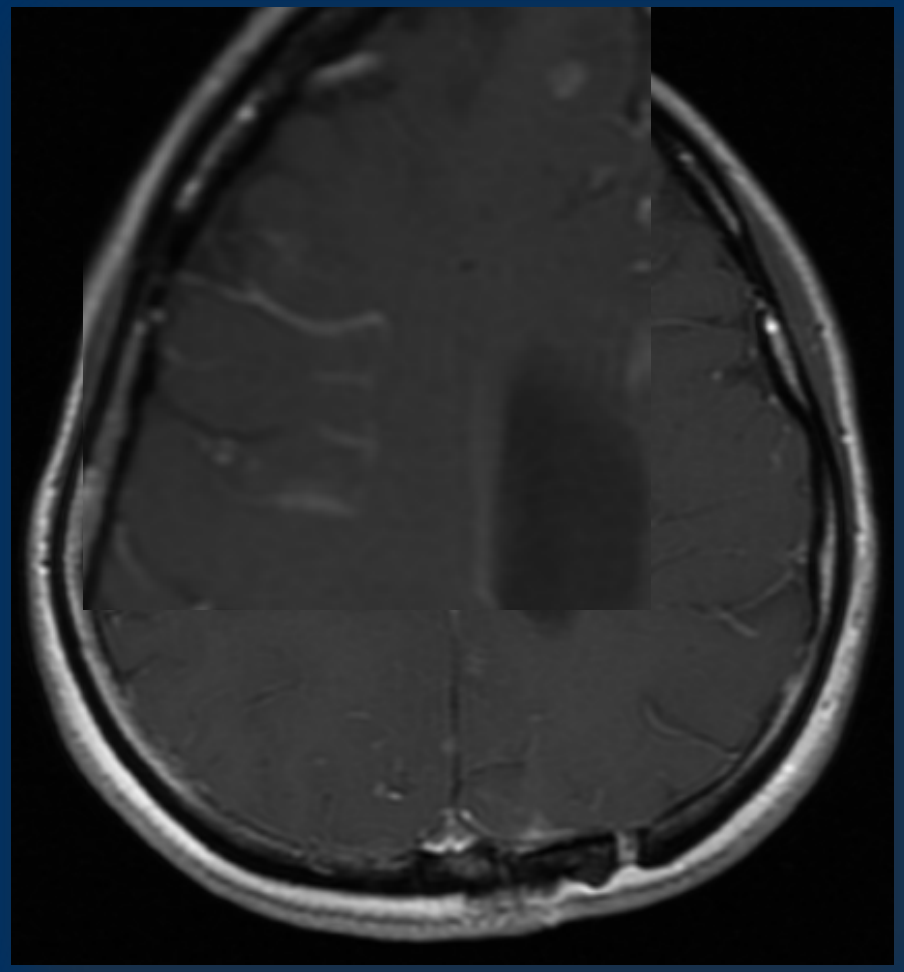



2 months



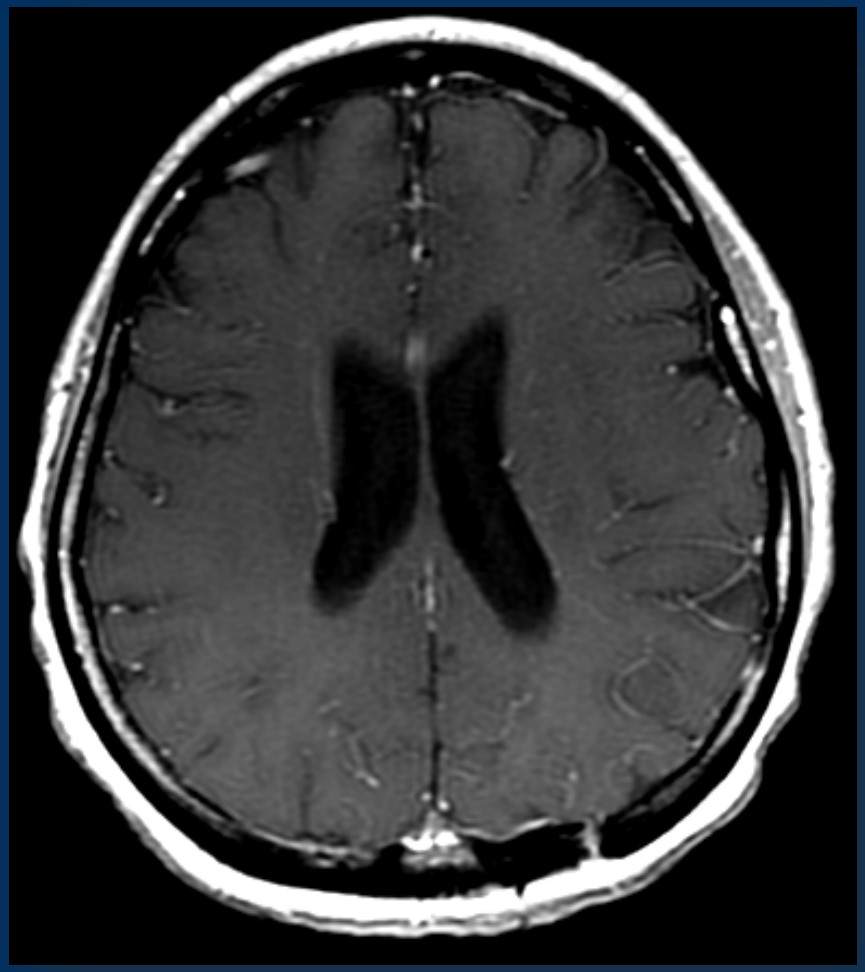

Images courtesy Stanford University.

# EGFR Mutant Case: Brain Imaging and LC



CSF = cerebrospinal fluid.

- Leptomeningeal disease is often best identified on T1 axial post-contrast series
- Often, subtle findings on imaging and diagnosis are based on radiographic findings, clinical presentation, and/or CSF analysis
- As people live longer on targeted therapies, we are seeing this rare metastasis more commonly



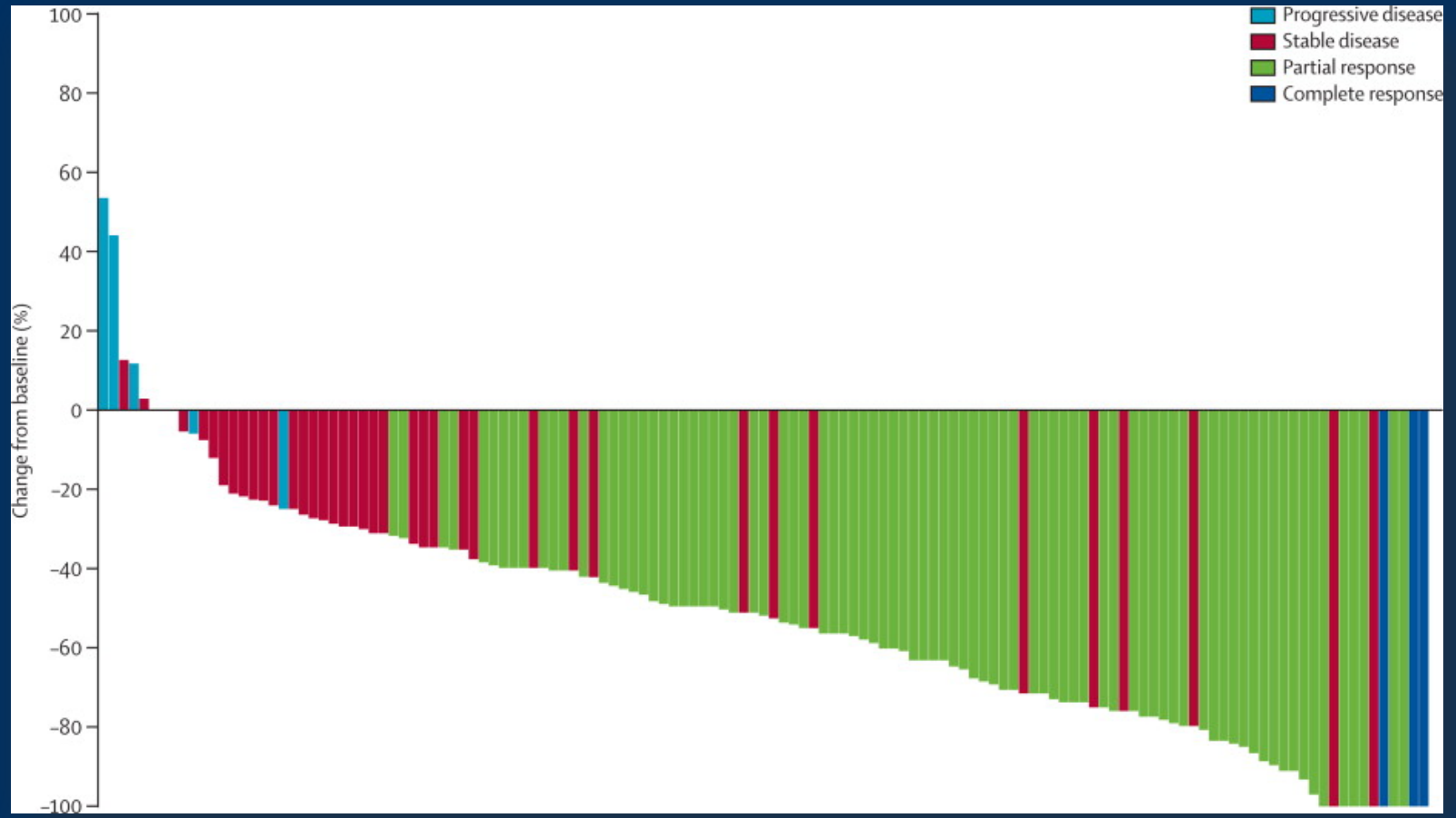
Images courtesy Stanford University.

# ALK Rearrangements: Background

- Found in 4%–5% of NSCLC adenocarcinoma patients
- More frequently seen in younger patients who are light or never smokers
- Males > females
- Predominantly a fusion of *ALK* with *EML-4* partner oncogene
- Felt to occur mutually exclusive of *EGFR* mutations

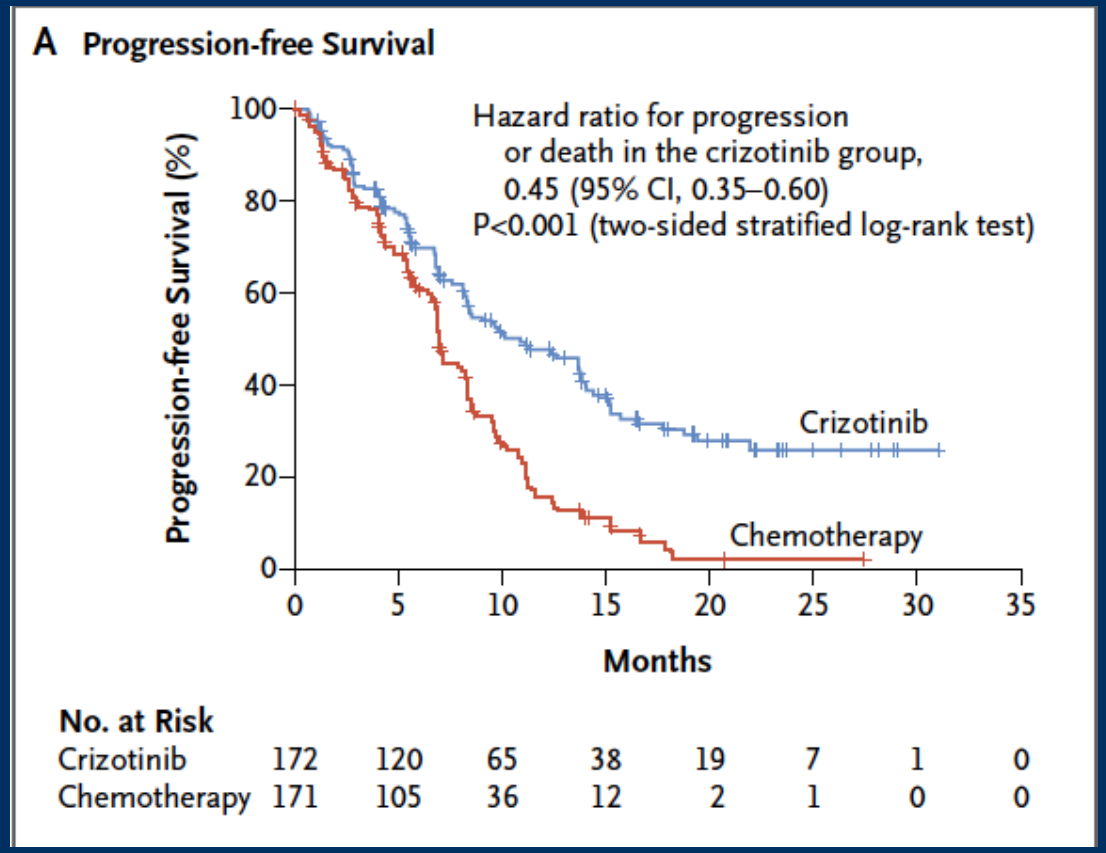
Soda M, et al. *Nature* 2007;448:561-6; Shaw AT, et al. *J Clin Oncol* 2009;27:4247-53.

# Crizotinib in ALK+ Patients: Phase I Study




Camidge DR, et al. *Lancet Oncol* 2012;13:1011-9.

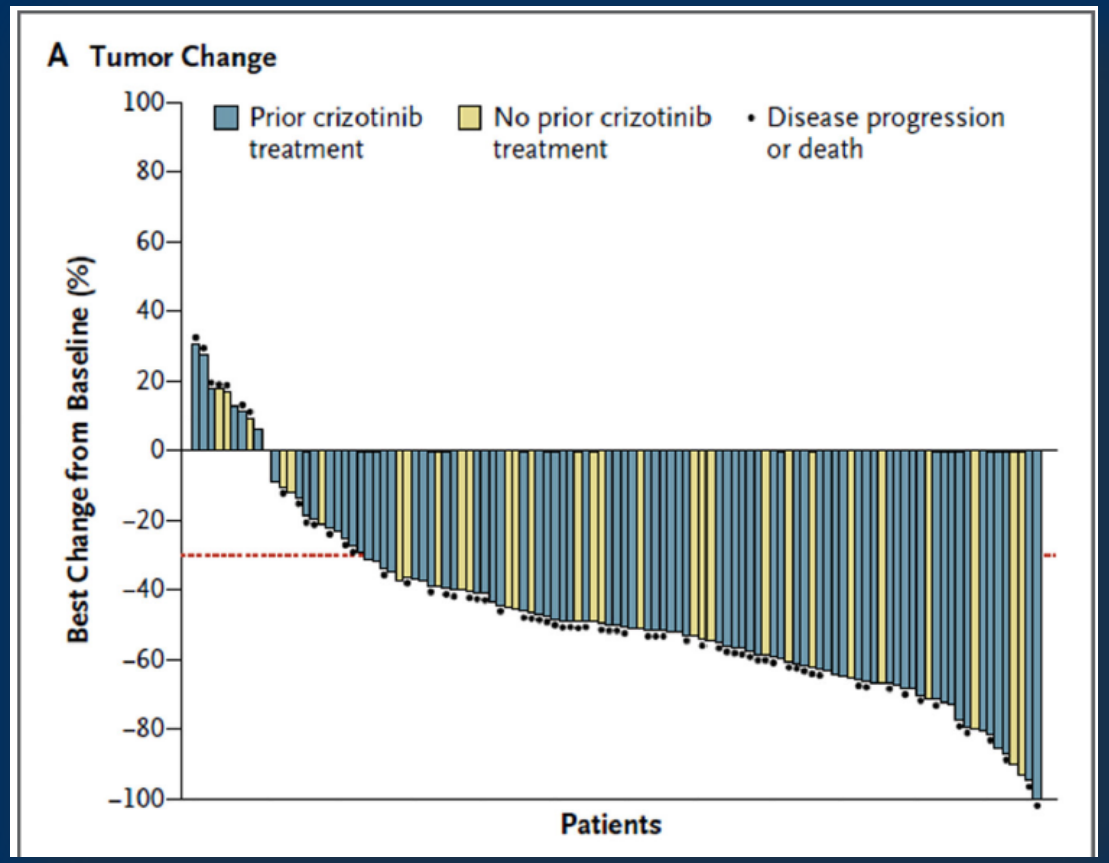
# PROFILE 1014: Crizotinib vs. Pemetrexed/ Platinum in Advanced *ALK*+ NSCLC




- Phase III (N = 343) study of *ALK*+ patients with nonsquamous NSCLC and no prior systemic treatment for advanced disease

Solomon BJ, et al. *N Engl J Med* 2014;371:2167-77.

# Ceritinib in *ALK*+ Lung Cancer




- Ceritinib is a novel ALK inhibitor with greater potency compared with crizotinib
- Phase I study
- Antitumor activity is independent of prior ALK-inhibitor therapy

Shaw AT, et al. *N Engl J Med* 2014;370:1189-97.

# Alectinib in Crizotinib-Refractory *ALK*+ NSCLC: Phase II Studies

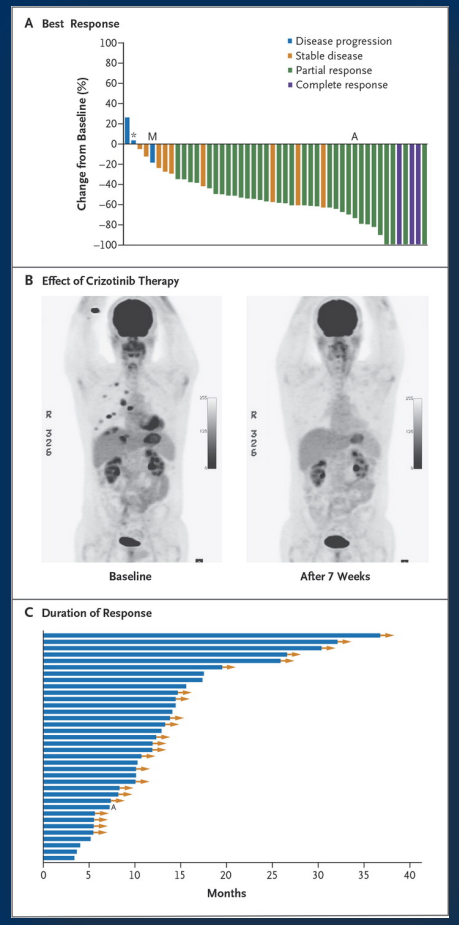
| Outcome | Ou (N = 138)[1] | Shaw (N = 87)[2] |
|---|---|---|
| ORR % | 50 | 48 |
| Prior chemo | 45 | NR |
| CNS metastasis | 57 | 75 |
| PFS (months) | 8.9 | 8.1 |
| Median DOR | 11.2 | 13.5 |
| CNS DCR | 83 | 89 |

In December 2015, the FDA approved alectinib for patients with *ALK*+, metastatic NSCLC who have progressed on or are intolerant to crizotinib

DCR = disease control rate; DOR = duration of response; FDA = US Food and Drug Administration.

[1]Ou S, et al. *J Clin Oncol*. 2016;34:661-8; [2]Shaw AT, et al. *Lancet Oncol*. 2016;17:234-42.

# Crizotinib in Patients With ROS1 Fusion

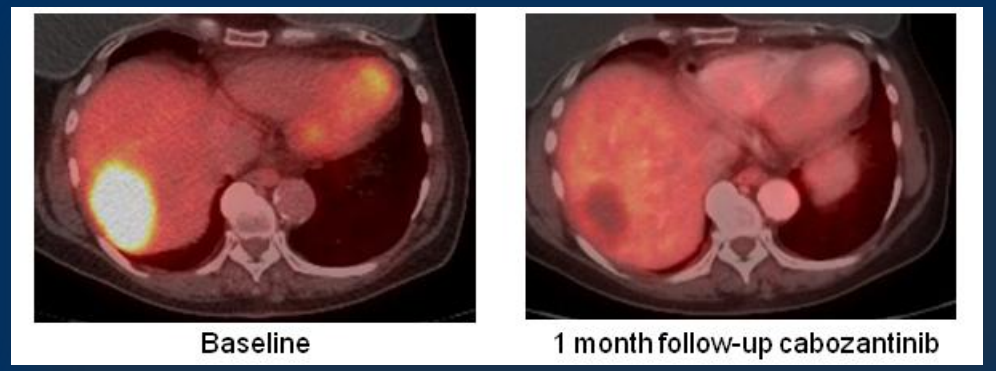



- In March 2016, the FDA approved crizotinib for patients with ROS1+, metastatic NSCLC
- 72% ORR
- 64% (23/36) ongoing responses
- Median DOR: 17.6 months
- Median PFS: 19.2 months

Shaw AT, et al. *N Engl J Med* 2014;371:1963-71.

# Other Genomic Targets

| Mutation | Drug |
|---|---|
| BRAF V600E | Dabrafenib[1]<br>Dabrafenib + trametinib[2] |
| RET fusion | Cabozantinib[3] |
| MET exon 14 splice mutation | Cabozantinib or crizotinib[4] |




[1]Planchard D, et al. *Ann Oncol* 2014;25:1-41; [2]Planchard D, et al. *J Clin Oncol* 2015;33 (suppl; abstr 8006); [3]Drilon AE, et al. *J Clin Oncol* 2015;33 (suppl; abstr 8007); [4]Paik PK, et al. *J Clin Oncol* 2015;33 (suppl; abstr 8021).

# Targeted Therapy: Summary

- Recently the FDA approved targeted therapies for the treatment of advanced NSCLC including osimertinib, ceritinib, alectinib, and crizotinib (new indication in *ROS1*)
- EGFR-TKI therapy is appropriate first-line therapy for patients with known EGFR-activating mutations
- ALK-targeted therapy is appropriate first-line therapy for patients with known EML4-ALK fusion protein
- Additional agents with activity in EGFR resistance and ALK resistance are under development
- Other targets being identified and active drugs found

# Immunotherapy in NSCLC

# Immunotherapy: Background

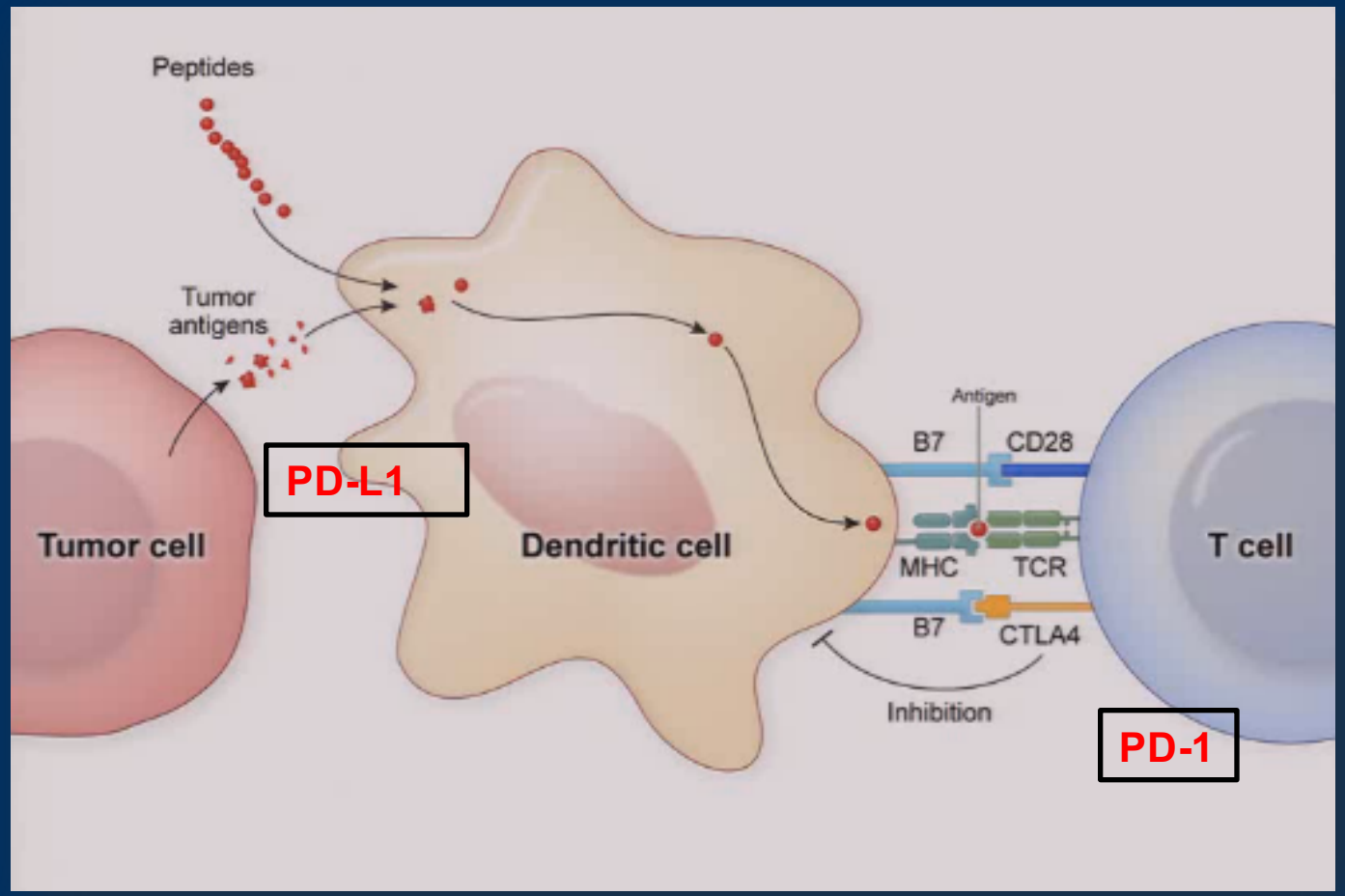
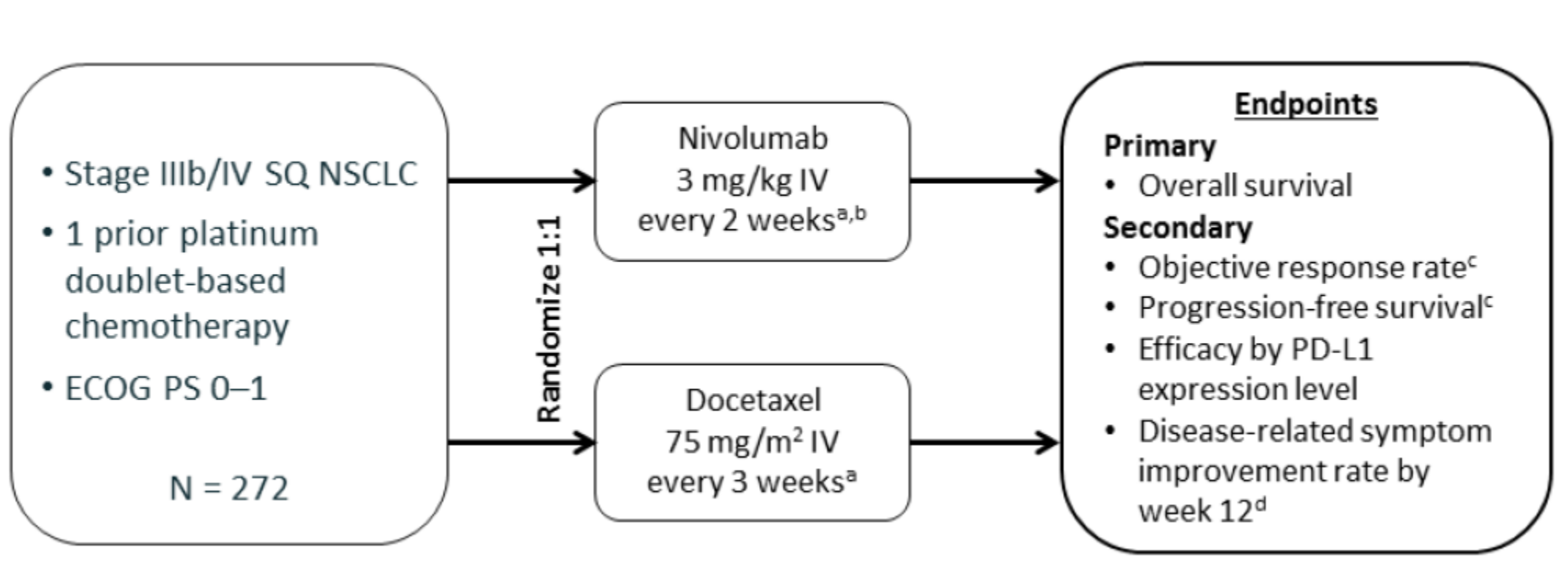


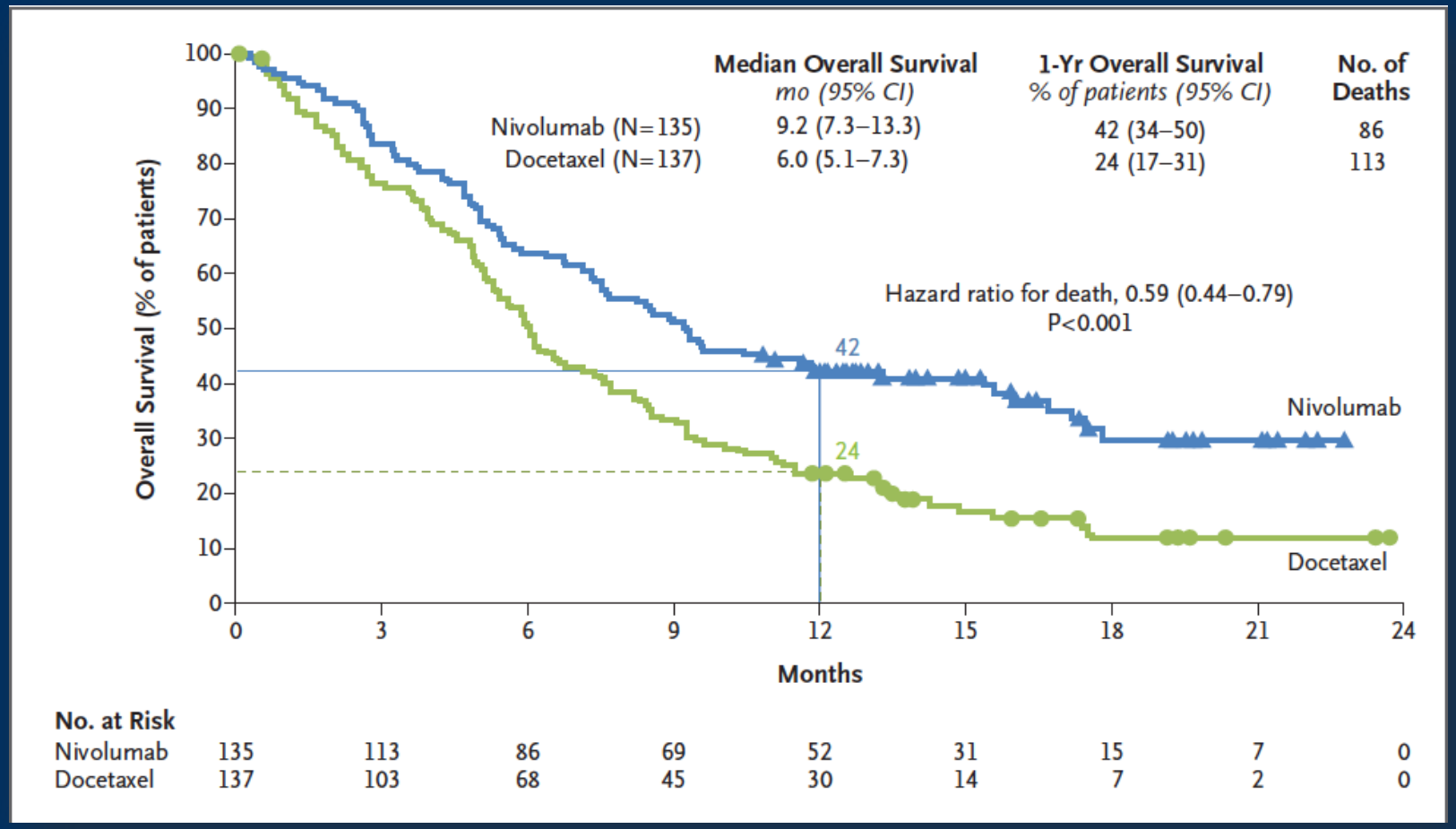

Image adapted from Raffit Hassan, MD, ASCO 2011 discussion (Chemoimmunotherapy: A Light in the Darkness)

# Checkmate-017: Nivolumab in Squamous NSCLC




Brahmer J, et al. *N Engl J Med*. 2015;373(2):123-35.

# Checkmate-017: Results



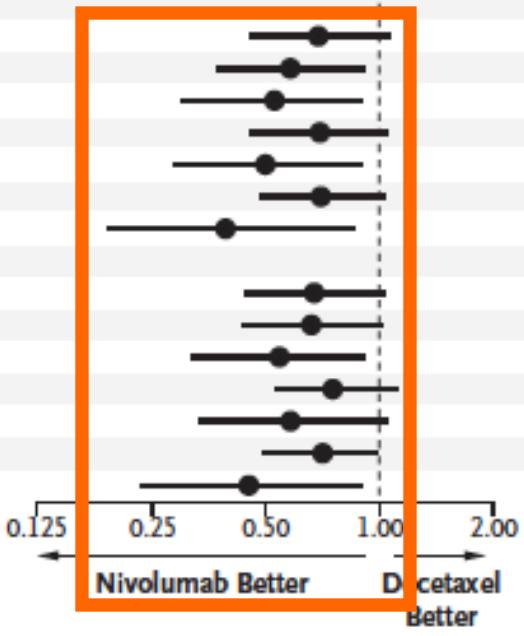

The FDA approved nivolumab in March 2015 for squamous NSCLC

Brahmer J, et al. *N Engl J Med* 2015;373:123-35.

# No Significant Interaction for PD-L1 and Response/PFS/OS in Squamous NSCLC

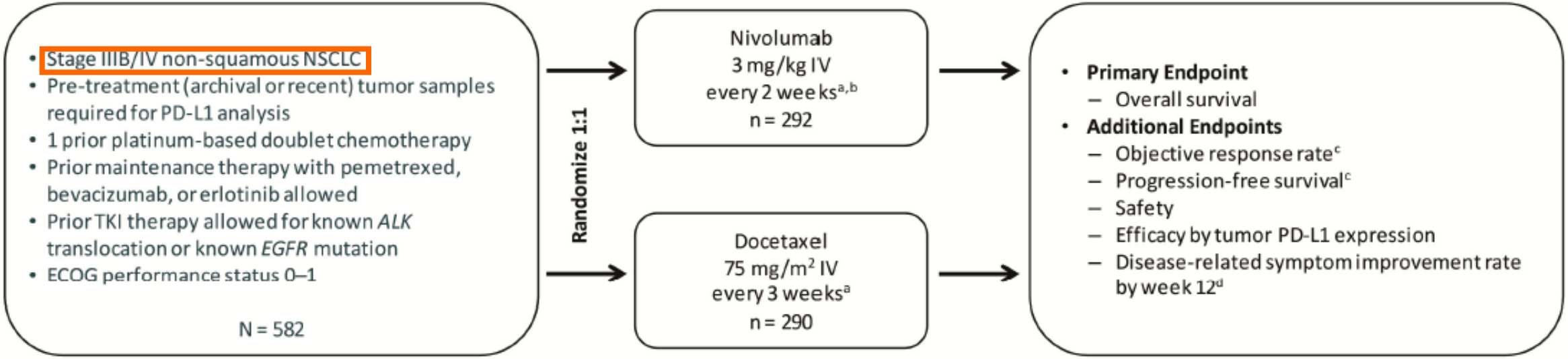
**C Overall and Progression-free Survival According to PD-L1 Expression Level**

| PD-L1 Expression Level | Nivolumab | Docetaxel | Unstratified Hazard Ratio (95% CI) |
|---|---|---|---|
| | *no. of patients* | | |
| Overall survival | | | |
| ≥1% | 63 | 56 | 0.69 (0.45–1.05) |
| <1% | 54 | 52 | 0.58 (0.37–0.92) |
| ≥5% | 42 | 39 | 0.53 (0.31–0.89) |
| <5% | 75 | 69 | 0.70 (0.47–1.02) |
| ≥10% | 36 | 33 | 0.50 (0.28–0.89) |
| <10% | 81 | 75 | 0.70 (0.48–1.01) |
| Not quantifiable at baseline | 18 | 29 | 0.39 (0.19–0.82) |
| Progression-free survival | | | |
| ≥1% | 63 | 56 | 0.67 (0.44–1.01) |
| <1% | 54 | 52 | 0.66 (0.43–1.00) |
| ≥5% | 42 | 39 | 0.54 (0.32–0.90) |
| <5% | 75 | 69 | 0.75 (0.52–1.08) |
| ≥10% | 36 | 33 | 0.58 (0.33–1.02) |
| <10% | 81 | 75 | 0.70 (0.49–0.99) |
| Not quantifiable at baseline | 18 | 29 | 0.45 (0.23–0.89) |



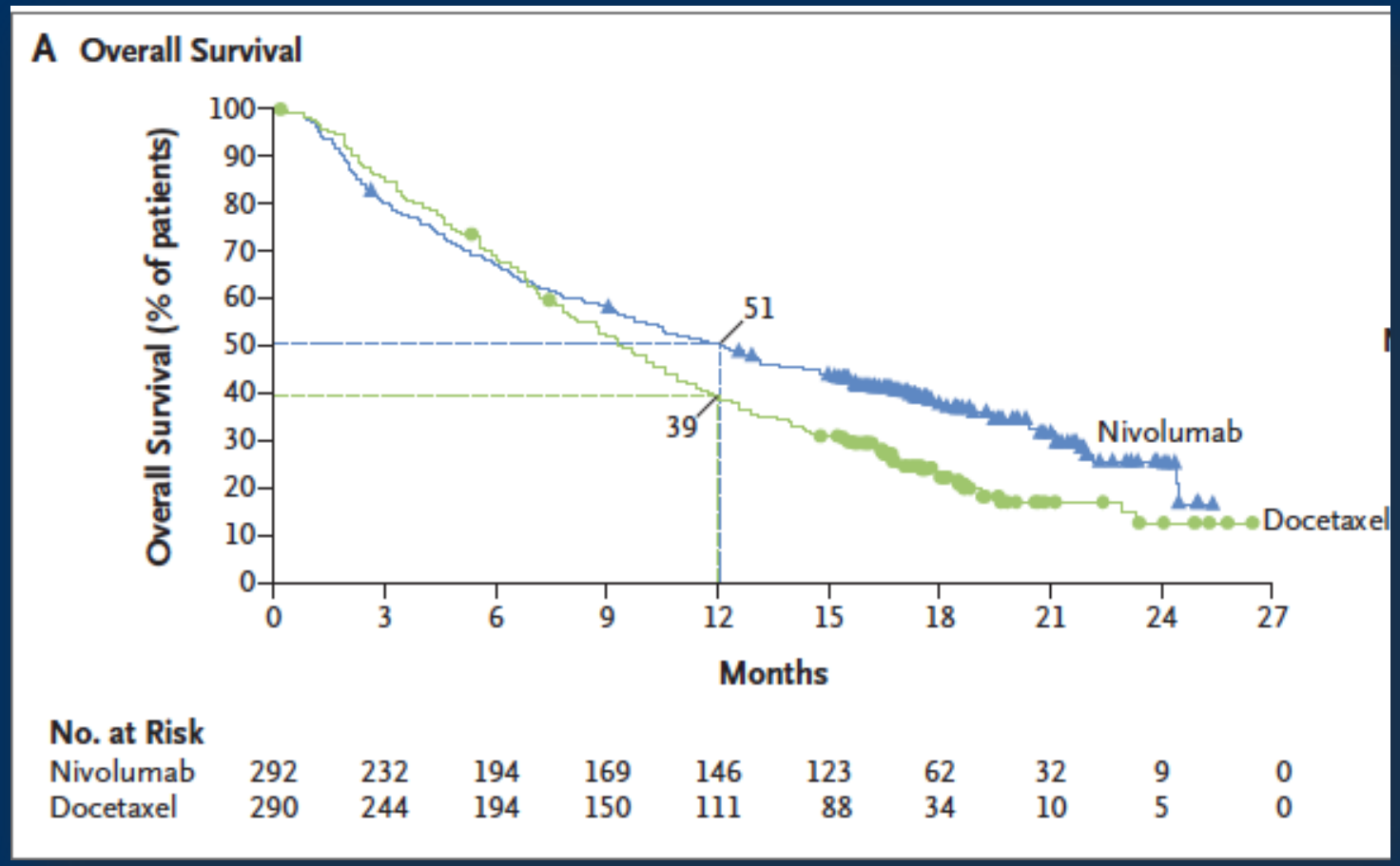

Brahmer J, et al. *N Engl J Med*. 2015;373(2):123-35.

# Checkmate-057: Nivolumab in Nonsquamous NSCLC




Borghaei H, et al. *N Engl J Med*. 2015;373(17):1627-39.

# Checkmate-057: Results

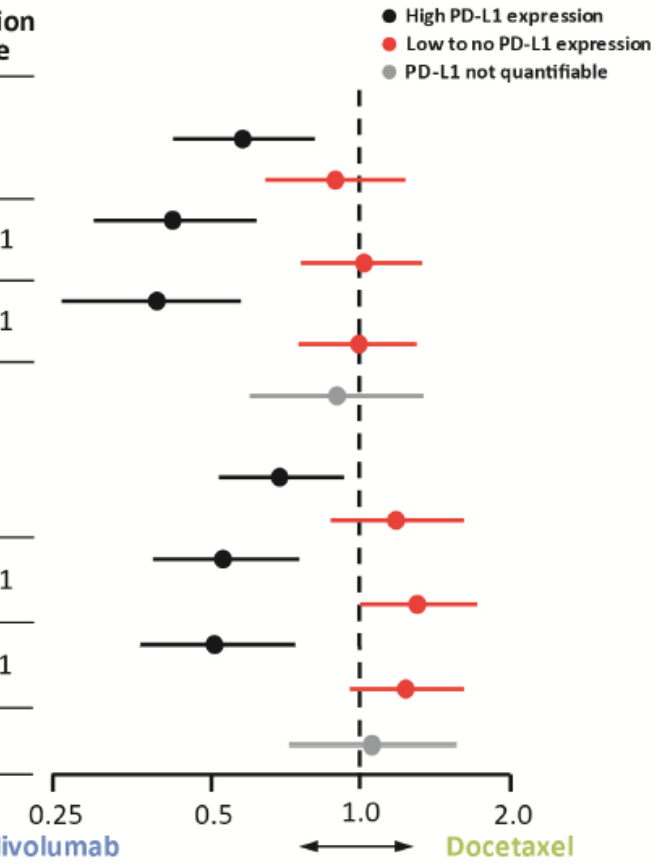



The FDA expanded approval of nivolumab in October 2015 to include nonsquamous NSCLC

Borghaei H, et al. *N Engl J Med* 2015;373:1627-39..

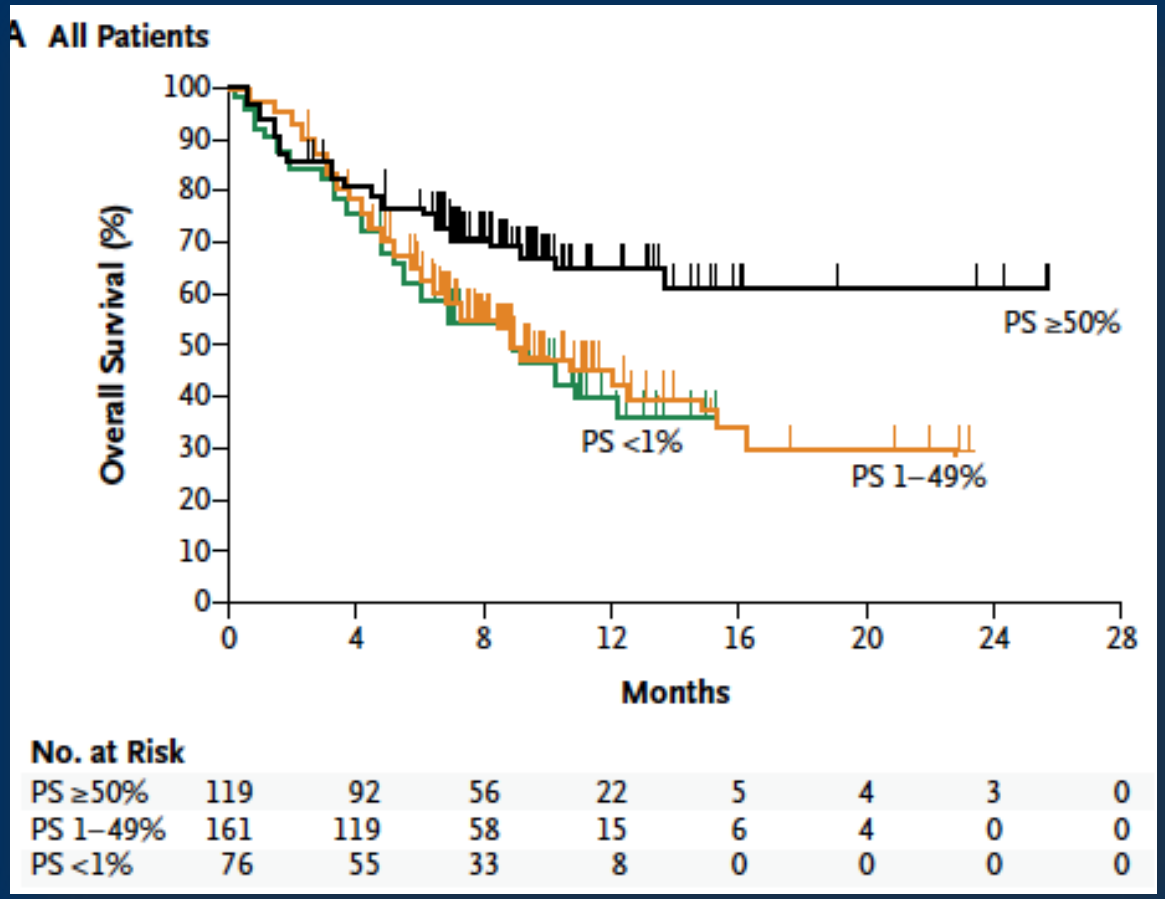
# Significant Interaction for PD-L1 and PFS/OS in Nonsquamous NSCLC

| PD-L1 expression level | Nivolumab n | Docetaxel n | Unstratified HR (95% CI) | Interaction *P*-value |
|---|---|---|---|---|
| **OS** | | | | |
| ≥1% | 123 | 123 | 0.59 (0.43, 0.82) | 0.06 |
| <1% | 108 | 101 | 0.90 (0.66, 1.24) | |
| ≥5% | 95 | 86 | 0.43 (0.30, 0.63) | <0.001 |
| <5% | 136 | 138 | 1.01 (0.77, 1.34) | |
| ≥10% | 86 | 79 | 0.40 (0.26, 0.59) | <0.001 |
| <10% | 145 | 145 | 1.00 (0.76, 1.31) | |
| Not quantifiable at baseline | 61 | 66 | 0.91 (0.61, 1.35) | |
| **PFS** | | | | |
| ≥1% | 123 | 123 | 0.70 (0.53, 0.94) | 0.02 |
| <1% | 108 | 101 | 1.19 (0.88, 1.61) | |
| ≥5% | 95 | 86 | 0.54 (0.39, 0.76) | <0.001 |
| <5% | 136 | 138 | 1.31 (1.01, 1.71) | |
| ≥10% | 86 | 79 | 0.52 (0.37, 0.75) | <0.001 |
| <10% | 145 | 145 | 1.24 (0.96, 1.61) | |
| Not quantifiable at baseline | 61 | 66 | 1.06 (0.73, 1.56) | |




Borghaei H, et al. *N Engl J Med*. 2015;373(17):1627-39.

# Keynote 001: Pembrolizumab in NSCLC




The FDA approved pembrolizumab in October 2015 for 2L+ NSCLC with companion diagnostic (PD-L1 IHC 22C3pharmDx test)

IHC = immunohistochemical.

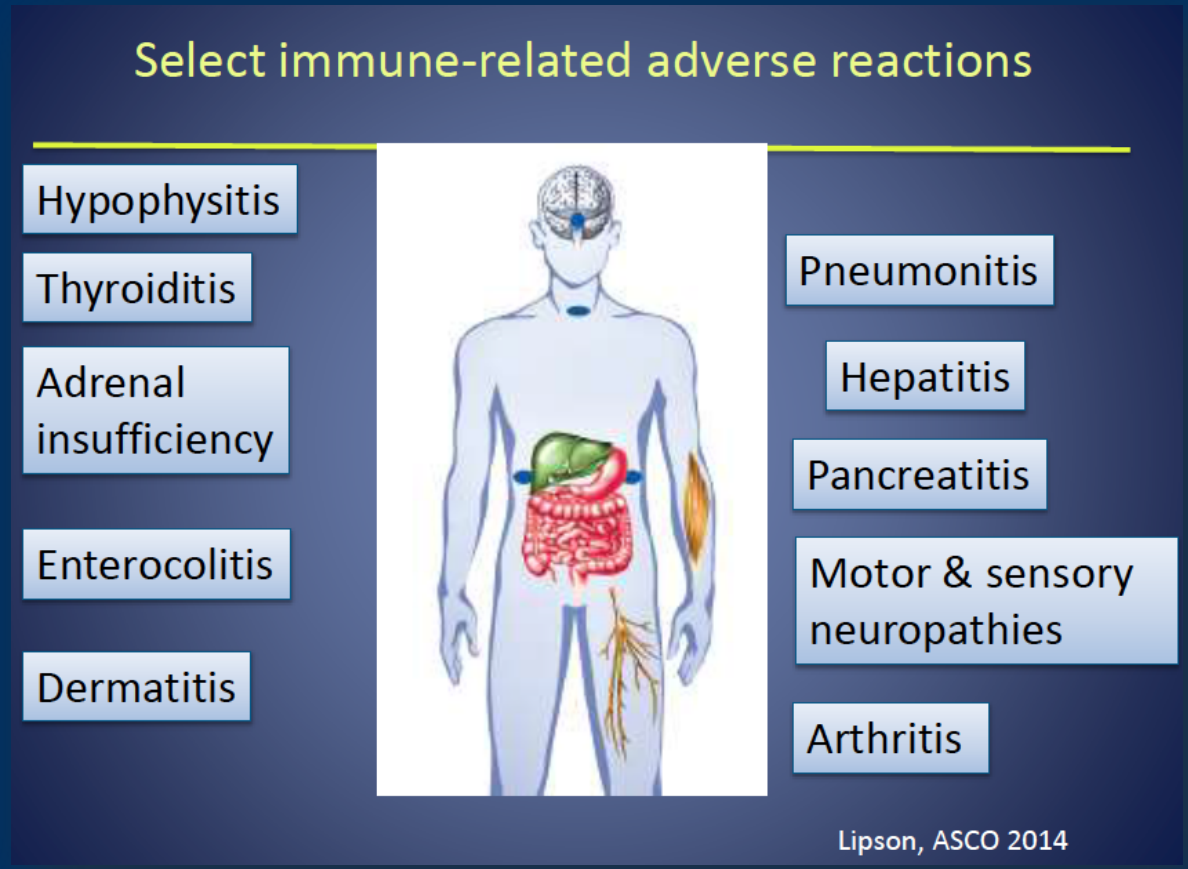
Garon EB et al. *N Engl J Med* 2015;372:2018-28.

# Keynote 024: Pembrolizumab as First-Line Treatment in NSCLC

- Published in NEJM on Oct 9, 2016
- Phase III study of 305 patients, previously untreated, with >50% PDL-1 expression (no EGFR or ALK)
  - Randomized to pembrolizumab vs. platinum doublet chemo
- Median PFS: 10.3 mo vs. 6.0 mo (HR=0.50, $p < .001$)
- OS at 6 months: 80.2% vs. 72.4% (HR=0.60, $p = .005$)
- RR: 44.8% vs. 27.8%
- Oct 24, 2016: FDA approved pembrolizumab for the treatment of patients with metastatic NSCLC with >50% PDL-1

Reck M, et al. *N Engl J Med* 2016;Oct 9:1-11.

# Summary of Immune-Mediated Toxicities




Lipson EJ, PD-1/PD-L1 & CTLA associated autoimmune toxicity. ASCO 2014. http://slides.asco.org/main/viewslide.asp?tpc=0&slide=250767&from=mtg&view=auth

# Immune Adverse Events

- Onset
  - Typically occurs 6–12 weeks after initiation of therapy
    - However, can occur within days of the first dose, after several months of treatment, and after discontinuation of therapy
- Patient complaints are autoimmune and drug-related until proven otherwise
  - Rule out infections, metabolic causes, tumor effects, etc.
- Early recognition, evaluation, and treatment are critical

# General Principles of Immune-Mediated Toxicities

| Grade | Treatment |
|---|---|
| Grade 1 | Supportive care; +/- withhold drug |
| Grade 2 | Withhold drug, consider re-dosing if toxicity resolves to ≤ grade 1; low-dose corticosteroids (prednisone 0.5 mg/kg/day or equivalent) if symptoms do not resolve within a week |
| Grade 3 | Discontinue drug; high-dose corticosteroids (prednisone 1–2 mg/kg/day or equivalent) tapered over ≥1 month once toxicity resolves to ≤ grade 1 |

# Case 3: Immunotherapy Case

- Mr. J is a 68-year-old man who initially presented in May 2015 with worsening low back pain radiating down his right leg and urinary incontinence x 1 month
- CT imaging revealed a large mass in the sacrum and ilium measuring 7 x 5 cm, extending into the spinal canal with associated pathologic fracture
- Biopsy was performed of RLL mass as well as partial sacrectomy of S2-4. Pathology was consistent with NSCLC, favoring adenocarcinoma (TTF1+); mutational profile was negative
- Stage IV (T2a, N2, M1b)

RLL = right lower lobe.

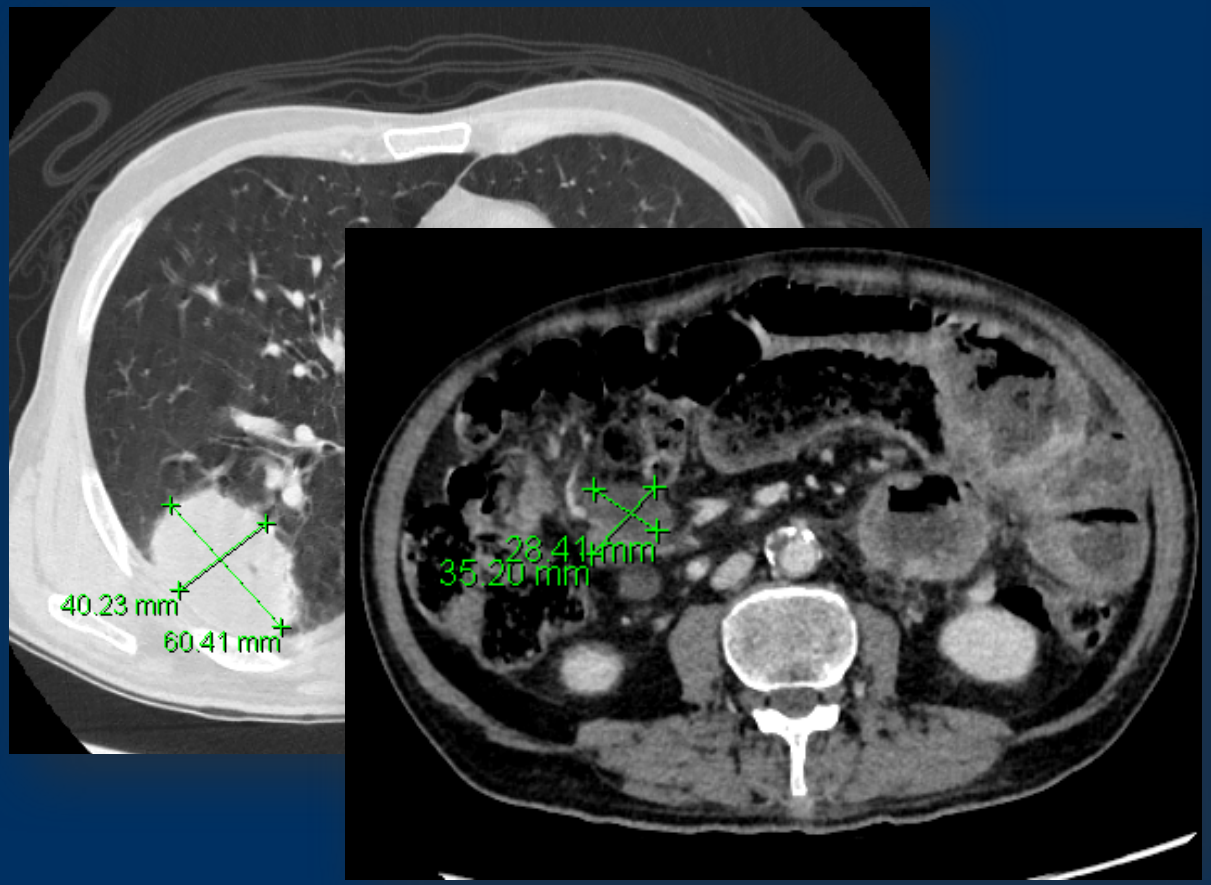
# Case 3 (cont)

- Mr. J. underwent palliative radiation to the sacrum and pelvis and started first-line therapy with carboplatin and pemetrexed with mixed response after 2 cycles and progression after 4 cycles
- Started therapy with nivolumab with additional radiation to right sacral metastasis due to recurrent pain
- Course was initially complicated by anemia related to GI bleed and then SBO

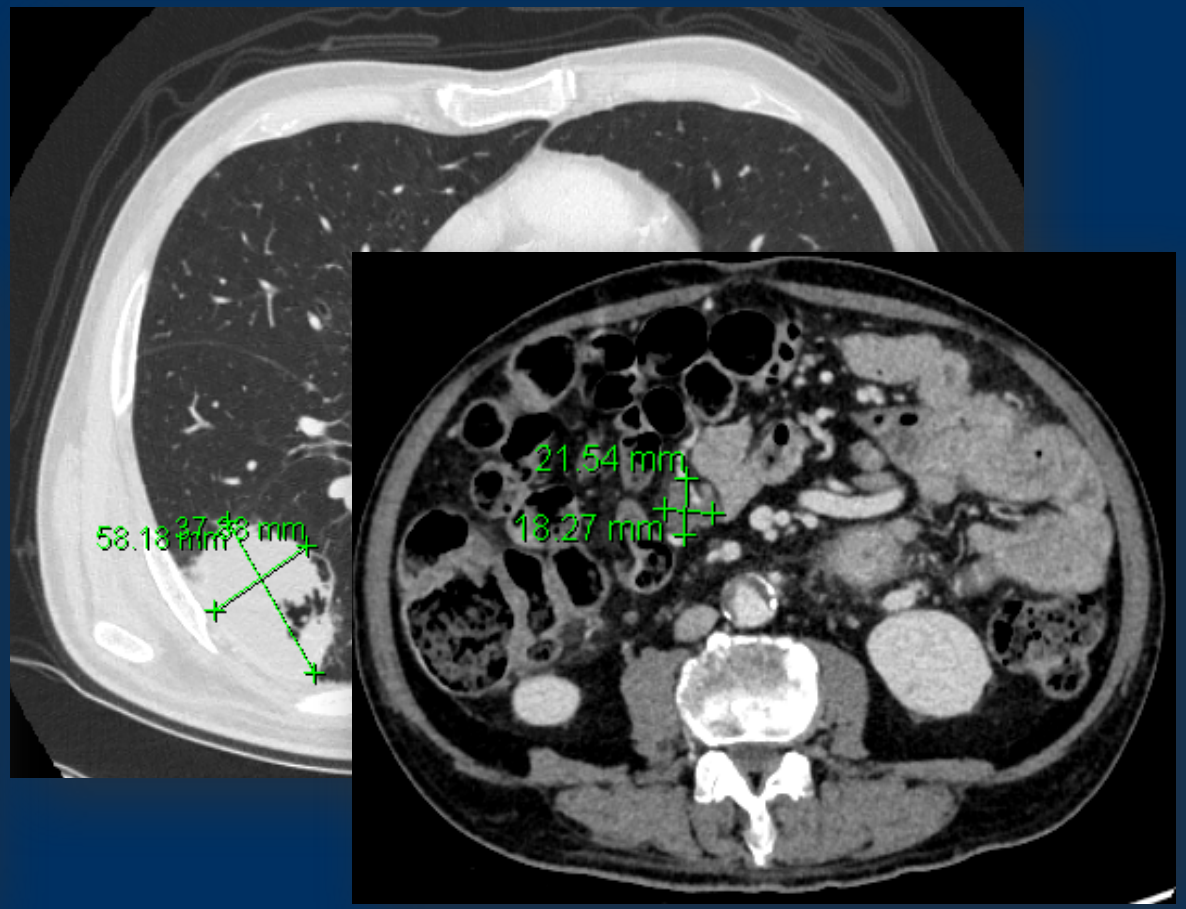
GI = gastrointestinal; SBO = small bowel obstruction.

# Case 3 (cont)

## Baseline




## After 3 Cycles




Images courtesy Stanford University.

# Immunotherapy: Summary

- Nivolumab (PD-1 inhibitor) approved for treatment of squamous and nonsquamous NSCLC
- Pembrolizumab (PD-1 inhibitor) approved for treatment of squamous and nonsquamous NSCLC
  - PD-L1 (IHC) is a “companion” diagnostic, required for clinical use of drug (PD-L1 IHC 22C3 pharmDx test)
- Tumor PD-L1 expression may be a useful biomarker (especially in nonsquamous) and other biomarkers are being explored (including resistance mechanisms)
- Other immune checkpoint inhibitors are being studied (including atezolizumab, a PDL-1 inhibitor) in NSCLC with promising results

# Overall Conclusions

- For the vast majority of patients, histology still guides therapeutic choice
- For patients with stage IV NSCLC and adenocarcinoma component, molecular testing is the standard of care
- Important to factor patient age/performance status and management of treatment-related AEs
- New FDA approvals for treatment of metastatic NSCLC: ramucirumab, nivolumab, pembrolizumab, osimertinib, necitumumab, alectinib, crizotinib (new indication for *ROS1*+ patients), atezolizumab