Oncology Grand Rounds
Non-Small Cell Lung Cancer

Nurse and Physician Investigators Discuss New Agents, Novel Therapies and Actual Cases from Practice

Wednesday, May 3, 2017
6:00 PM – 8:00 PM

Faculty

Kelly EH Goodwin, MSN, RN, ANP-BC
Melissa Johnson, MD
Geoffrey R Oxnard, MD
Mollie Reed, MSN, RN, ACNP-BC

Moderator

Neil Love, MD

Research To Practice®

Oncology Grand Rounds Series

Wednesday	**Non-Small Cell Lung Cancer** 6:00 PM – 8:00 PM
Thursday	**Cancer Immunotherapy** 6:00 AM – 7:30 AM
	Breast Cancer 12:15 PM – 1:45 PM
	Lymphomas and CLL 6:00 PM – 8:00 PM
Friday	**Myeloproliferative Neoplasms** 6:00 AM – 7:30 AM
	Ovarian Cancer 12:15 PM – 1:45 PM
	Gastrointestinal Cancers 6:00 PM – 8:00 PM

Oncology Grand Rounds: Themes

Identifying and understanding oncology clinical scenarios

- Key determining factors; natural history and treatment
- Evaluating and managing clinical symptoms
- Patient and caregiver education

Integrating new agents and treatment strategies into practice

- Benefits and risks
- Prevention, identification and management of side effects/toxicity
- Identifying patients at high risk for toxicity

Psychosocial issues in clinical oncology

- Caring for family and loved ones, including minor children and grandchildren
- Job satisfaction and disappointment
- The bond that heals

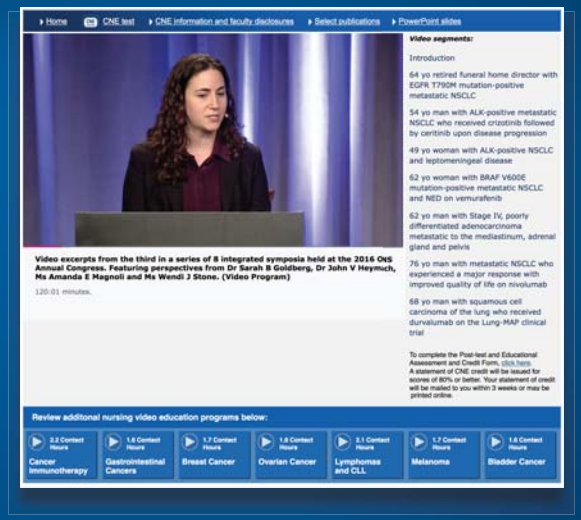
Novel Agents Approved by the FDA in the Past 9 Weeks		
Agent	**Approval Date**	**FDA-Approved Use on Approval Date**
Telotristat ethyl	February 28th	In combination with somatostatin analogue (SSA) therapy for the treatment of patients with carcinoid syndrome diarrhea inadequately controlled by SSA therapy alone
Ribociclib	March 13th	In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with ER-positive, HER2-negative advanced or metastatic breast cancer
Avelumab	March 23rd	For the treatment of patients with metastatic Merkel cell carcinoma
Niraparib	March 27th	For the maintenance treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer
Brigatinib	April 28th	For the treatment of patients with ALK-positive metastatic non-small cell lung cancer who have progressed on or are intolerant to crizotinib
Midostaurin	April 28th	For the treatment of newly diagnosed FLT3-positive acute myeloid leukemia in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation
Durvalumab	May 1st	For the treatment of patients with locally advanced or metastatic urothelial carcinoma

https://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/ucm537040.htm


Early-Stage NSCLC
Locally Advanced NSCLC
EGFR-Mutant Metastatic NSCLC
ALK-Mutant Metastatic NSCLC
Other Targetable Mutations in Metastatic NSCLC
Pan-Wild-Type Nonsquamous Metastatic NSCLC
Pan-Wild-Type Squamous Metastatic NSCLC

About the Enduring Program

- The proceedings from this 7-part CNE series will be video recorded and used in a virtual meeting archive including a downloadable version of the slides.



- An email will be sent to all attendees when the web activity is available.
- To learn more about our education programs visit our website, www.ResearchToPractice.com

Download the RTPLive app on your smartphone or tablet to access program information, including slides being presented during the program:

www.ResearchToPractice.com/RTPLiveApp

Make the Meeting Even More Relevant to You

Submit a challenging case or question for discussion during the program.

Email to **DrNeilLove@ResearchToPractice.com**

Text to **(786) 759-1458**

(Your phone number will remain confidential and will not be disclosed.)

If you are unable to text or email, please complete a question/comment card located on your conference table and drop it in one of the designated bins located throughout the meeting room.

Make the Meeting Even More Relevant to You

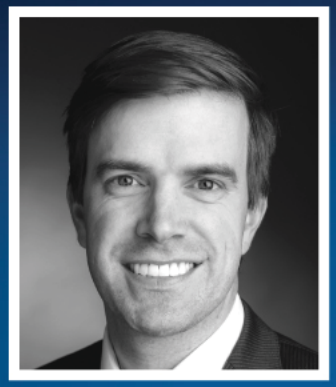
Join the conversation by sharing photos and videos using the hashtag #RTPLive

Facebook **@researchtopractice**

Twitter **@DrNeilLove**

Instagram **@researchtopractice**

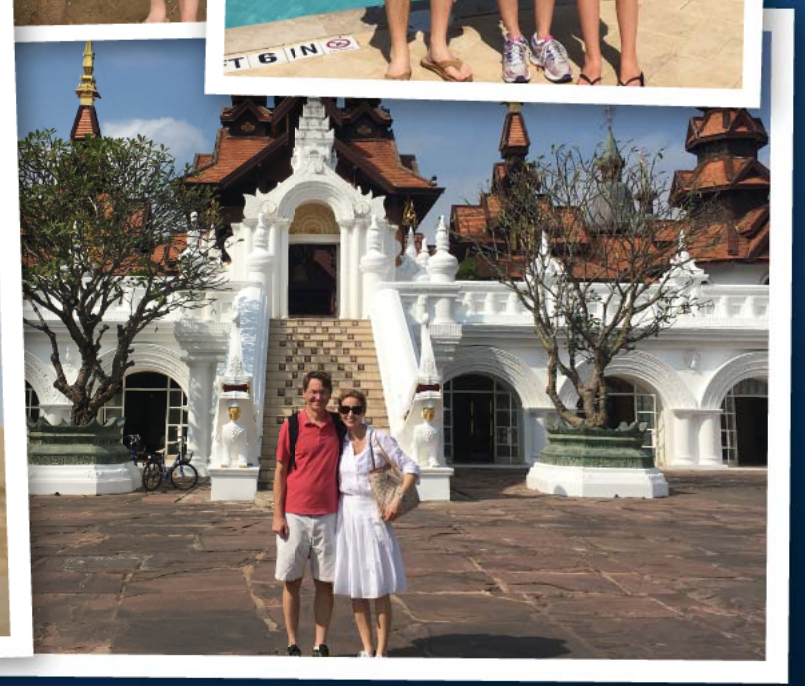
And get here early to participate in a brief video interview, where you can tell us about your interesting cases, thought-provoking questions and what you find rewarding about oncology nursing. You may even see your post on the big screen during the events!



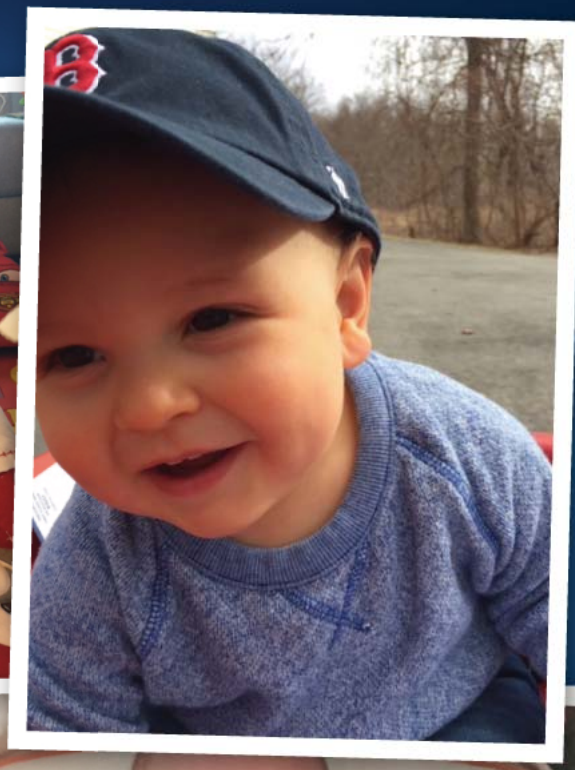
Geoffrey R Oxnard, MD
Dana-Farber Cancer Institute
Boston, Massachusetts

Melissa Johnson, MD
Sarah Cannon Research Institute
Nashville, Tennessee

Mollie Reed, MSN, RN, ACNP-BC
Sarah Cannon Research Institute
Nashville, Tennessee



Kelly EH Goodwin, MSN, RN, ANP-BC
Massachusetts General Hospital
Boston, Massachusetts



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Module 1:
Overview of NSCLC

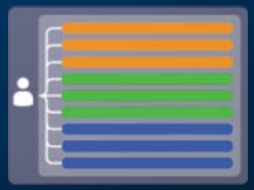
Overview of Lung Cancer

- Estimated number of new cases and deaths in 2016:
  - New cases = 222,500
  - Deaths = 155,870
- Stage at diagnosis (percent of patients who present with):
  - Stage I disease = 13%
  - Stage II disease = 7%
  - Stage III disease = 25%
  - Stage IV disease = 55%
- 53% men, 47% women
- Five-year survival estimates (2005-2011) = 18%

Cancer Facts and Figures 2017; cruk.org/cancerstats

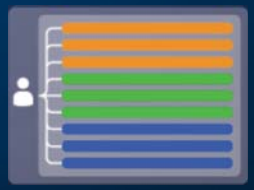
Critical Scenario/Pathway Factors

- Disease stage
  - Adjuvant
  - Locally advanced
  - Metastatic
- Disease symptomatology
- Patient performance status
- Tobacco-related comorbidities
- Tumor histology
  - Squamous
  - Nonsquamous



Critical Scenario/Pathway Factors

- Tumor assays up-front and after recurrence
  - Key genomic alterations and incidence
    - EGFR (T790M), ALK, ROS1, BRAF, RET, MET exon 14, HER2
  - Tissue versus plasma versus urine assays
    - Single assays versus multiplex
  - Tissue assays for PD-L1 status and use of checkpoint inhibitors (CIs)

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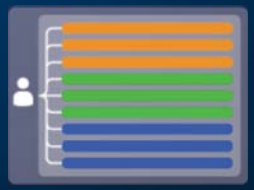
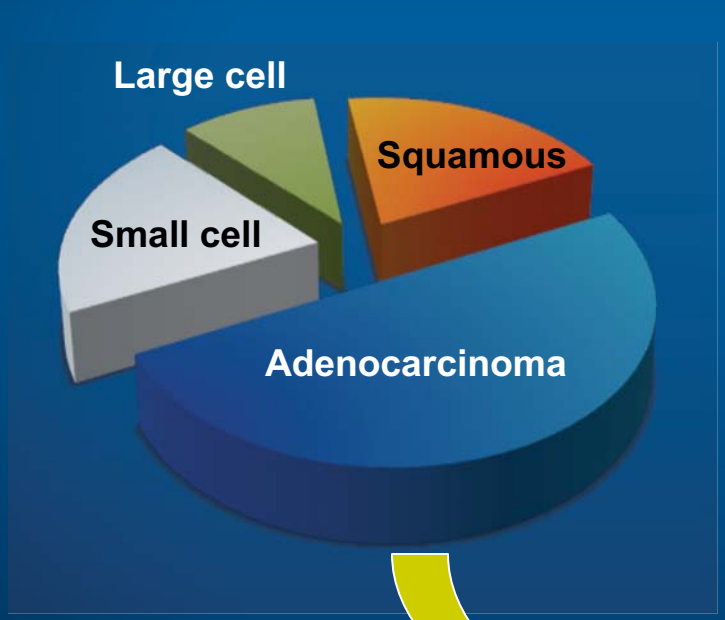
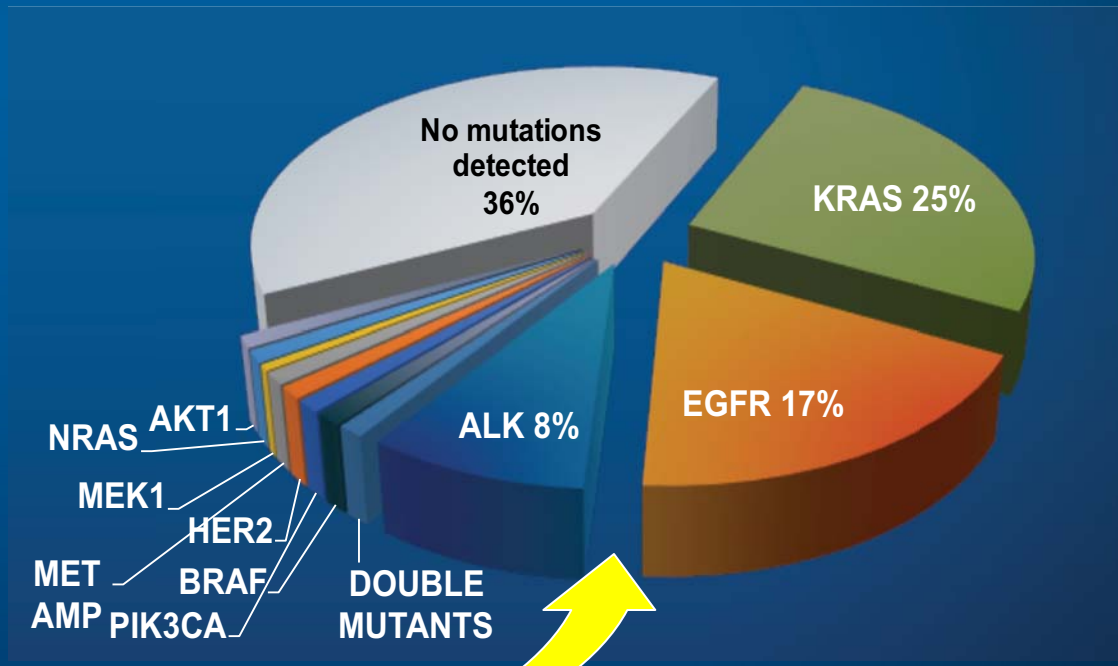
Classes of Approved Systemic Treatments

- **Chemotherapy**
  - Platinums, taxanes, pemetrexed, gemcitabine, vinorelbine
- **Biologics**
  - Bevacizumab, necitumumab, ramucirumab
- **Targeted Therapies**
  - Erlotinib, gefitinib, afatinib, osimertinib, crizotinib, ceritinib, alectinib, brigatinib
- **Checkpoint Inhibitors**
  - Pembrolizumab, nivolumab, atezolizumab



Evolving Identification of Molecular Subsets in Lung Adenocarcinoma





Kris MG et al. *JAMA* 2014;311(19):1998-2006.

Module 2:
Early-Stage NSCLC


Early-Stage NSCLC
Locally Advanced NSCLC
EGFR-Mutant Metastatic NSCLC
ALK-Mutant Metastatic NSCLC
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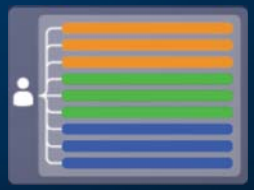
Key Considerations

- Selection of therapy:
  - Cisplatin versus carboplatin
  - Platinum partners: pemetrexed, taxanes, gemcitabine
- Targeted therapy in patients with genomic tumor alterations



Common Adjuvant Therapy Regimens for Nonsquamous and Squamous NSCLC

- Cisplatin + vinorelbine
- Cisplatin + docetaxel
- Cisplatin + gemcitabine
- Cisplatin + etoposide
- Cisplatin + pemetrexed (nonsquamous NSCLC only)

Note: Carboplatin may be used in select patients

NCCN NSCLC Guidelines, version 5. 2017

Module 3:
Locally Advanced NSCLC


Early-Stage NSCLC
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EGFR-Mutant Metastatic NSCLC
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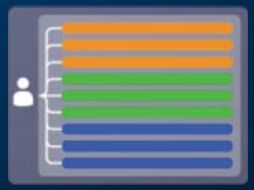
Key Considerations

- Selection of chemotherapy with radiation therapy
- Management of radiation toxicity: esophagitis



Concurrent Chemotherapy/Radiation Therapy Regimens for Locally Advanced NSCLC

- Cisplatin + etoposide with RT
- Cisplatin + vinblastine with RT
- Carboplatin + paclitaxel with RT
- Cisplatin or carboplatin + pemetrexed with RT
  - (Nonsquamous NSCLC only)

NCCN NSCLC Guidelines, version 5. 2017

Module 4:
EGFR-Mutant Metastatic NSCLC


Early-Stage NSCLC
Locally Advanced NSCLC
EGFR-Mutant Metastatic NSCLC
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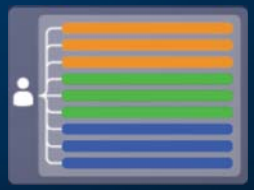
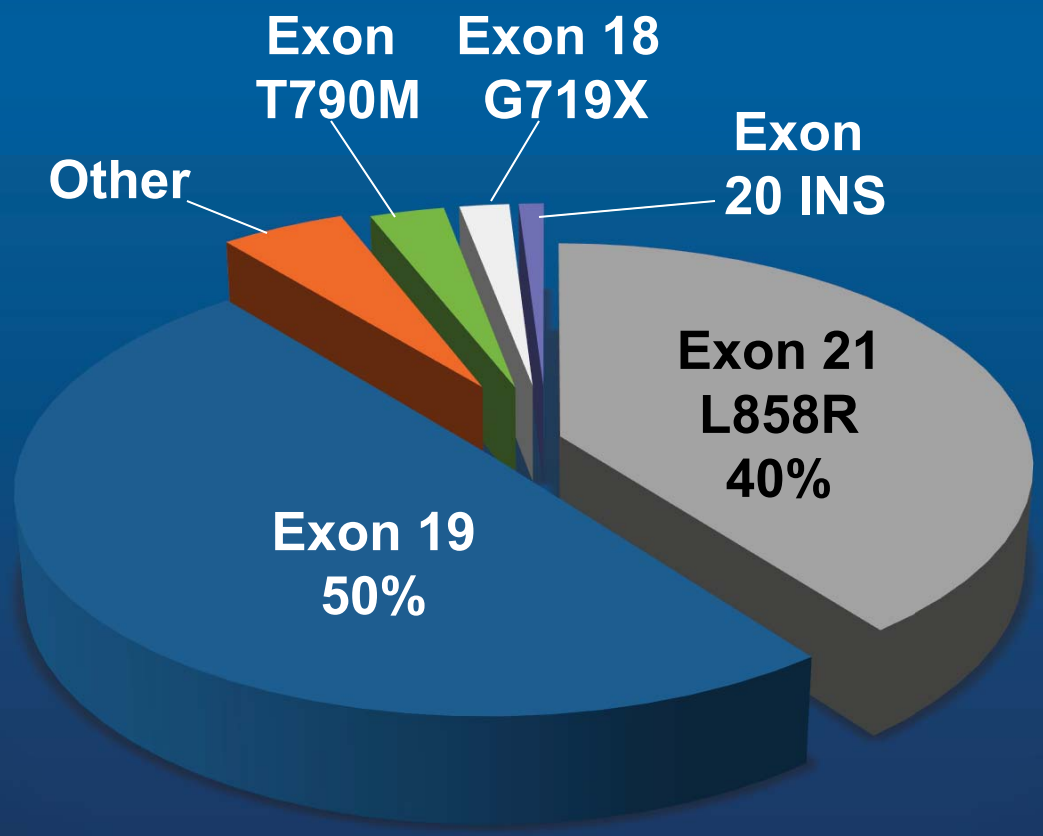
Key Considerations for First-Line Therapy in Patients with EGFR Mutations

- Type of EGFR mutation
- Presence of brain metastases
- First-line treatment
  - EGFR TKI versus chemotherapy
  - EGFR TKI versus checkpoint inhibitor
- Choice of up-front EGFR TKI: Relative efficacy and side-effect profiles of erlotinib, afatinib, gefitinib
- Approach to patients with severe tumor symptomatology



Common EGFR Mutations at First Diagnosis



http://www.egfr-mutation.com/how-to-test/mutation-testing-methods.html

First-Line Treatment Options in EGFR Mutation-Positive NSCLC

- **Erlotinib**
  - 150 mg/d (PO) until disease progression (PD) or unacceptable toxicity[1-3]
- **Afatinib**
  - 40 mg/d (PO) until PD or unacceptable toxicity[4-5]
- **Gefitinib**
  - 250 mg/d (PO) until PD or unacceptable toxicity[6]

[1] Zhou C et al. *Lancet Oncol* 2011;12(8):735-42; [2] Rosell R et al. *Lancet Oncol* 2012;13(3):239-46; [3] Seto T et al. *Lancet Oncol* 2014;15(11):1236-44; [4] Sequist LV et al. *J Clin Oncol* 2013;31(27):3327-34; [5] Wu YL et al. *Lancet Oncol* 2014;15(2):213-22; [6] Ichiihara E et al. *J Thorac Oncol* 2015;10(3):486-91.

In general, what would be your likely initial treatment recommendation for a younger patient with metastatic adenocarcinoma of the lung with an EGFR exon 19 deletion mutation and a TPS of 60%?

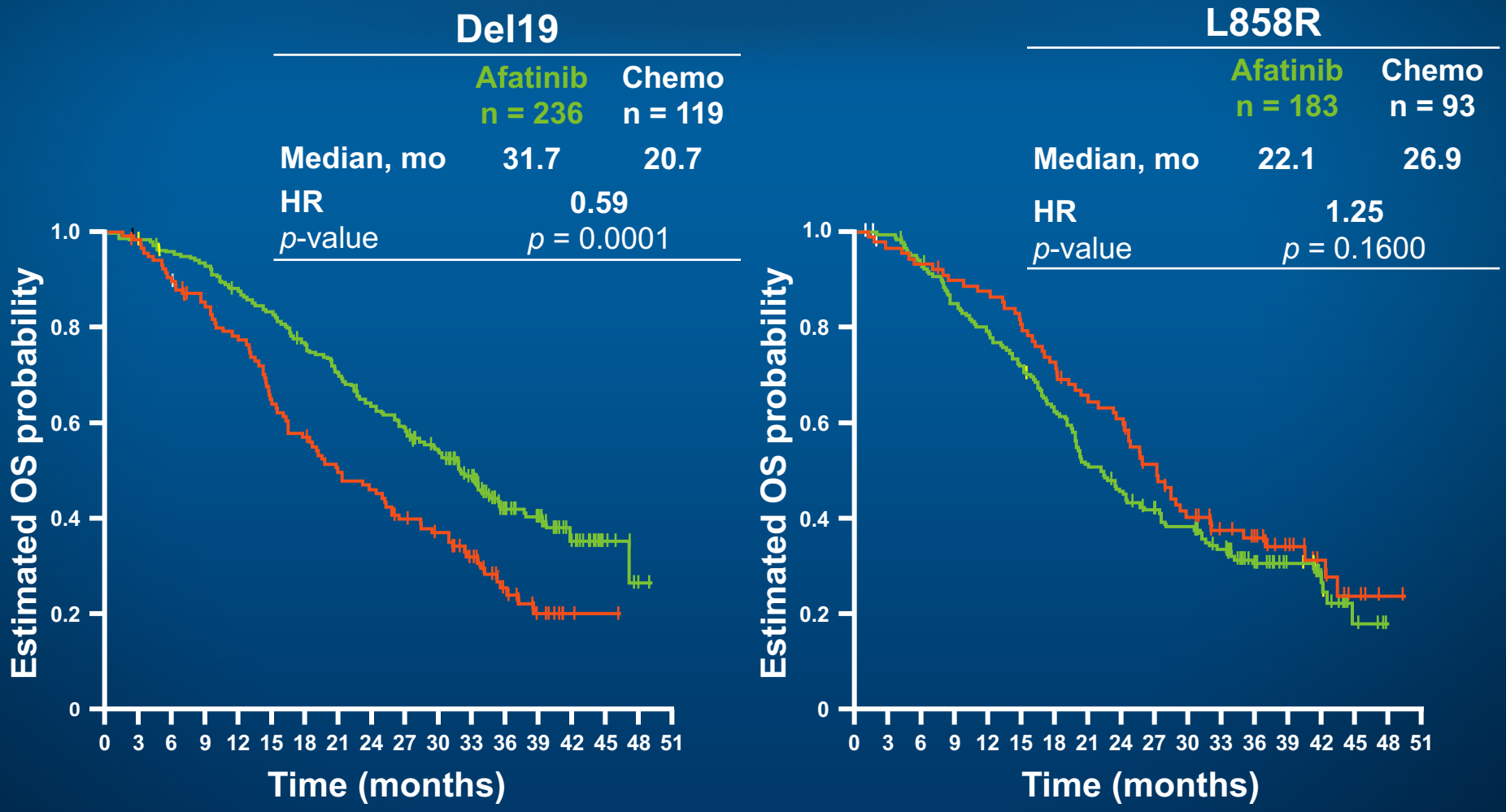
 RAMASWAMY GOVINDAN, MD	Erlotinib
 JOEL W NEAL, MD, PHD	Erlotinib
 GREGORY J RIELY, MD, PHD	Erlotinib
 JULIE R BRAHMER, MD	Afatinib
 COREY J LANGER, MD	Afatinib
 HEATHER WAKELEE, MD	Erlotinib

Studies of First-Line EGFR Inhibitors vs Chemo

Study	N	Arms	Response rate (%)	Med PFS (mo)	HR
IPASS	261	Gefitinib	71%	9.6	0.48
		Carbo/paclitaxel	47%	6.3	
WJTOG 3405	228	Gefitinib	62%	9.2	0.49
		Cis/docetaxel	31%	6.3	
NEJ 002	194	Gefitinib	74%	10.4	0.36
		Carbo/paclitaxel	31%	5.5	
OPTIMAL	165	Erlotinib	83%	13.1	0.16
		Carbo/gem	36%	4.6	
EURTAC	174	Erlotinib	58%	9.7	0.37
		Cis or carbo + doce or gem	15%	5.2	
LUX-Lung 3	345	Afatinib	69%	11.1 (*13.6*)	0.58
		Cis/pem	44%	6.9 (*6.9*)	0.47

Courtesy of Alice T Shaw, MD, February 11, 2017

LUX-Lung 3 and 6: Combined Overall Survival Analysis by Mutation Category



Yang CH et al. *Lancet Oncol* 2015;16:141-51.

LUX-Lung 7: Efficacy of First-Line Afatinib versus Gefitinib for EGFR Mutation-Positive NSCLC

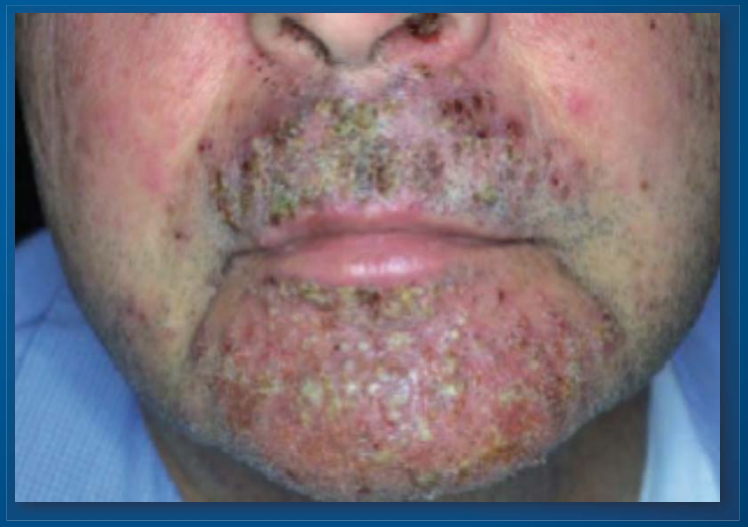
Outcome	Afatinib (n = 160)	Gefitinib (n = 159)	HR, *p*-value
Median PFS	11.0 mo	10.9 mo	0.74, 0.017
Median OS	27.9 mo	24.5 mo	0.86, 0.258

- The trend favoring afatinib was consistent across prespecified subgroups including deletion 19 and L858R populations
- Low rates of treatment discontinuation due to drug-related AEs were observed on each arm (6% each)

Paz-Ares L et al. *Ann Oncol* 2017;28(2):270-7.

Skin Rash with Tyrosine Kinase Inhibitors

- Most frequent dermatologic side effect reported is acneiform eruption
- Affects mainly face, upper chest and/or back
- Also known as acne, acneiform skin reaction/rash, follicular rash and maculopapular skin rash



Ricciardi S et al. *Clin Lung Cancer* 2009;10(1):28-35.

Prophylaxis of Dermatologic Toxicities with EGFR Inhibitors

Within first 6 weeks of EGFR TKI administration

- Employ proactive approach
- Thick, alcohol-free emollient cream
- Sunscreen ≥SPF15, preferably with zinc oxide or titanium dioxide
- Good hygiene

Lynch TJ et al. *Oncologist* 2007;12:610-21.

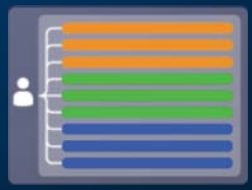
Management of Dermatologic Toxicities with EGFR Inhibitors

- Hydrocortisone 1% or 2.5% cream
- Clindamycin 1% gel
- Pimecrolimus 1% cream
- Doxycycline 100 mg BID
- Minocycline 100 mg BID
- Methylprednisolone dose pack
- Dose reduction, interruption or discontinuation

Lynch TJ et al. *Oncologist* 2007;12:610-21.

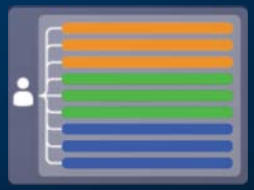
Key Considerations for Patients Progressing on First-Line EGFR TKI

- Continuation of EGFR TKI in patients who are stable with disease progression only on imaging
- Typical clinical course and management approach after first relapse, including T790M mutation testing
- Use of tissue, plasma and urine mutation assays
- Management of T790M mutation-negative and mutation-positive disease
- Osimertinib: Efficacy and tolerability, CNS efficacy



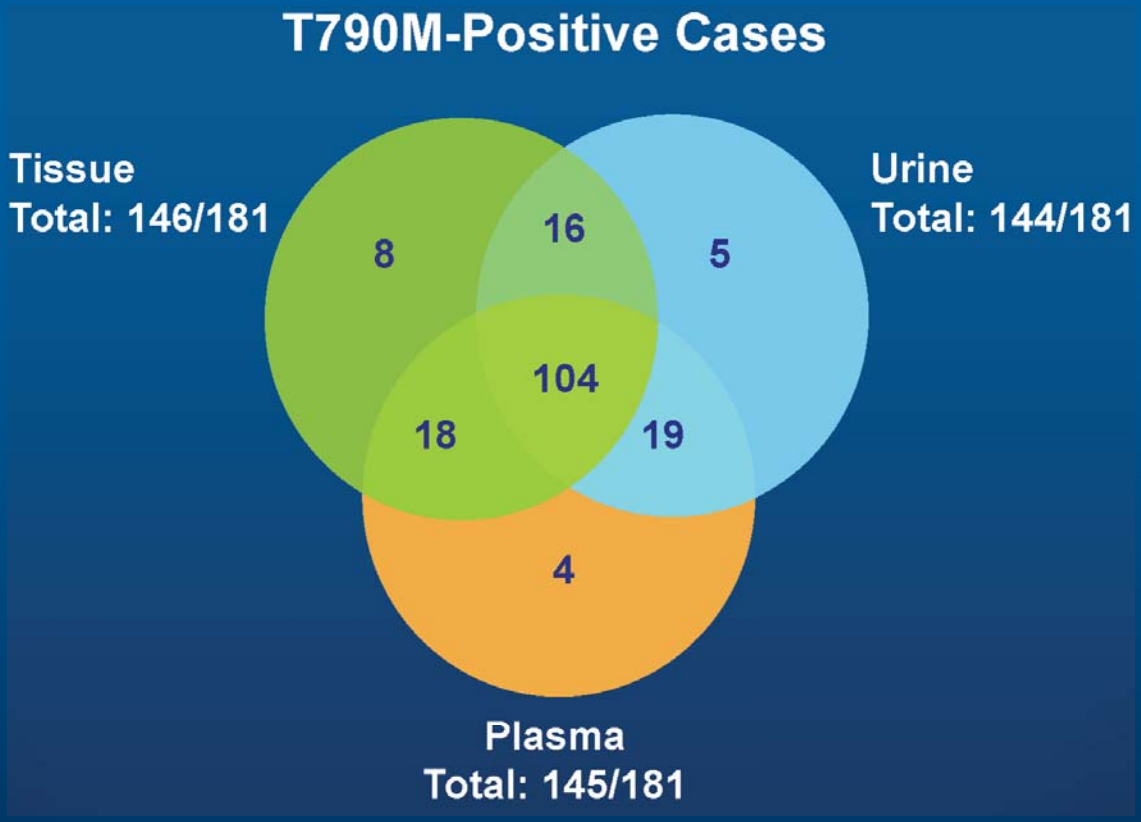
Treatment Options for Patients with T790M-Negative Metastatic NSCLC After Progression on an EGFR TKI

- Continue erlotinib and add bevacizumab
- Chemotherapy +/- bevacizumab
- Afatinib/cetuximab
- Pembrolizumab
- Nivolumab
- Atezolizumab



Plasma, Tissue and Urine Identify Unique and Overlapping Subsets of T790M-Positive Disease

181 samples with matched pretreatment T790M results in plasma, tissue and urine



- 57% were positive by all 3 sample types

Wakelee HA et al. *Proc ASCO* 2016;Abstract 9001.

VOLUME 34 · NUMBER 28 · OCTOBER 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

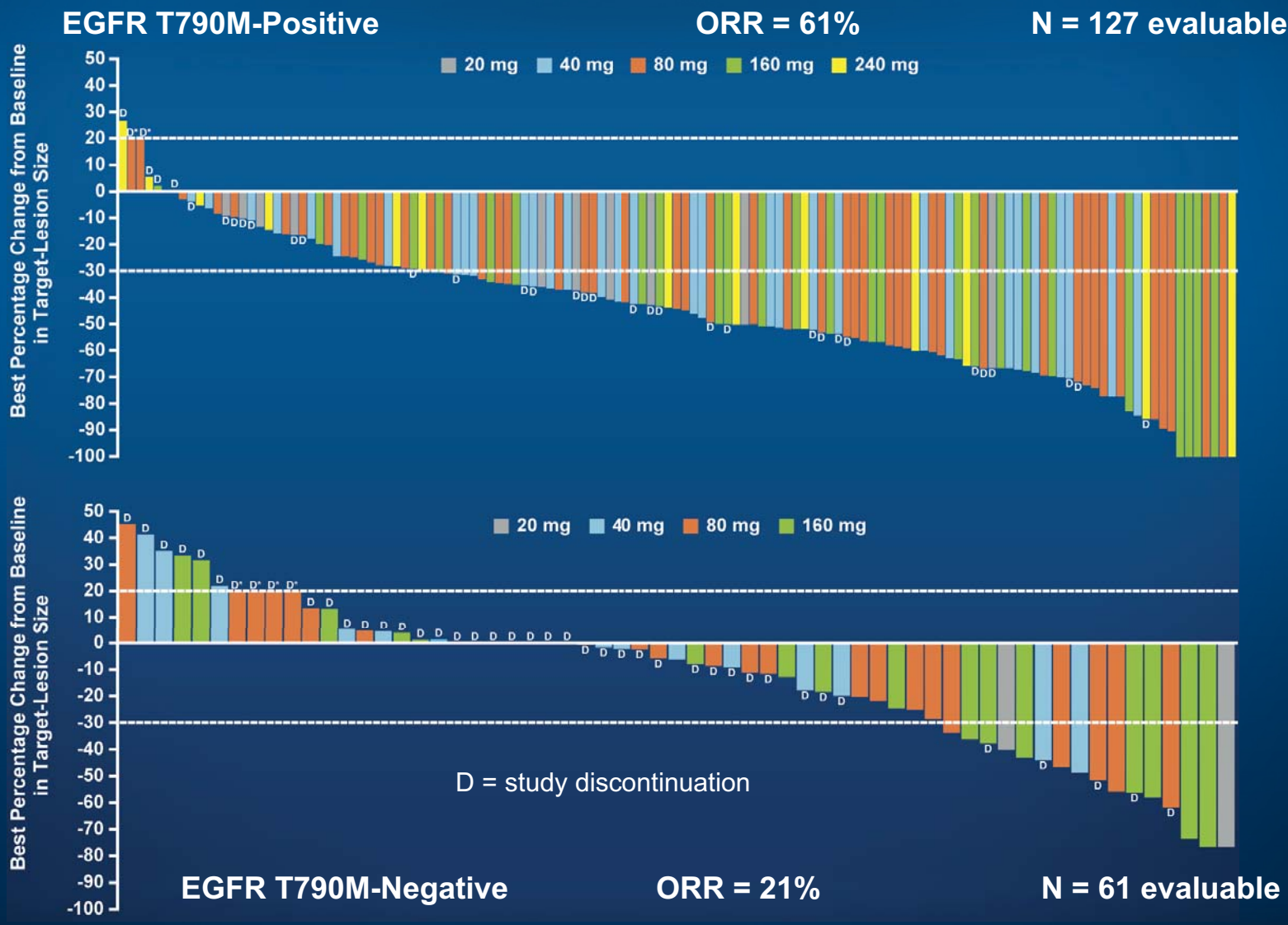
ORIGINAL REPORT

Association Between Plasma Genotyping and Outcomes of Treatment With Osimertinib (AZD9291) in Advanced Non–Small-Cell Lung Cancer

Geoffrey R. Oxnard, Kenneth S. Thress, Ryan S. Alden, Rachael Lawrance, Cloud P. Paweletz, Mireille Cantarini, James Chih-Hsin Yang, J. Carl Barrett, and Pasi A. Jänne

Oxnard GR et al. *J Clin Oncol* 2016;34(28):3375-82.

Change in Tumor Size with Osimertinib in EGFR TKI-Resistant T790M Mutation-Positive and -Negative NSCLC



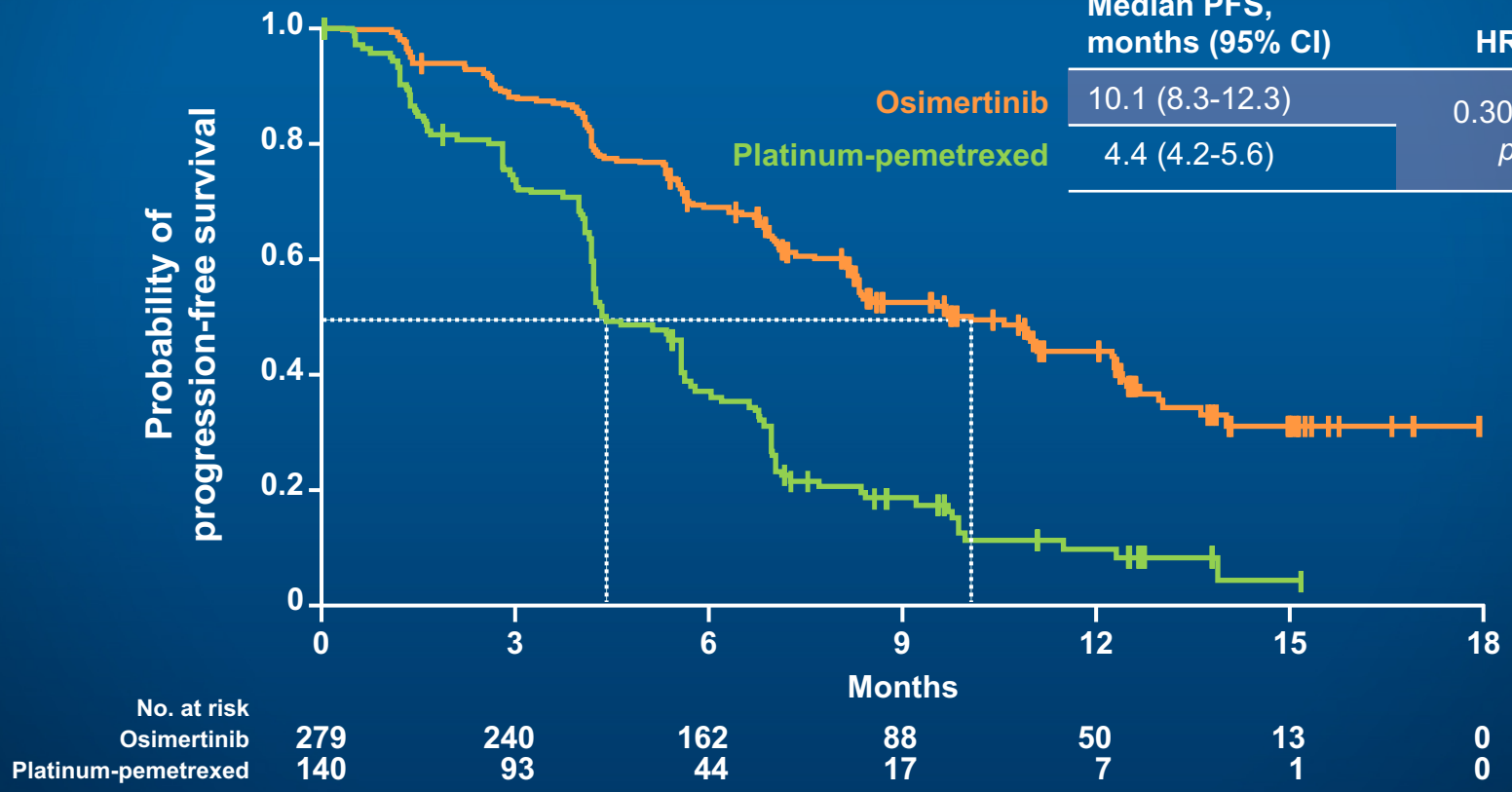
Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99.

Select Adverse Events with Osimertinib

	Osimertinib (N = 253)	
	Any grade	Grade 3-5
Diarrhea	47%	2%
Nausea	22%	<0.5%
Rash	40%	1%
Pruritus	19%	0%
Decreased appetite	21%	1%
Constipation	16%	0%
Hyperglycemia	6 (2.4%)	
QT interval prolongation	11 (4.3%)	
Pneumonitis-like event	6 (2.4%)	

Jänne PA et al. *N Engl J Med* 2015;372(18):1689-99.

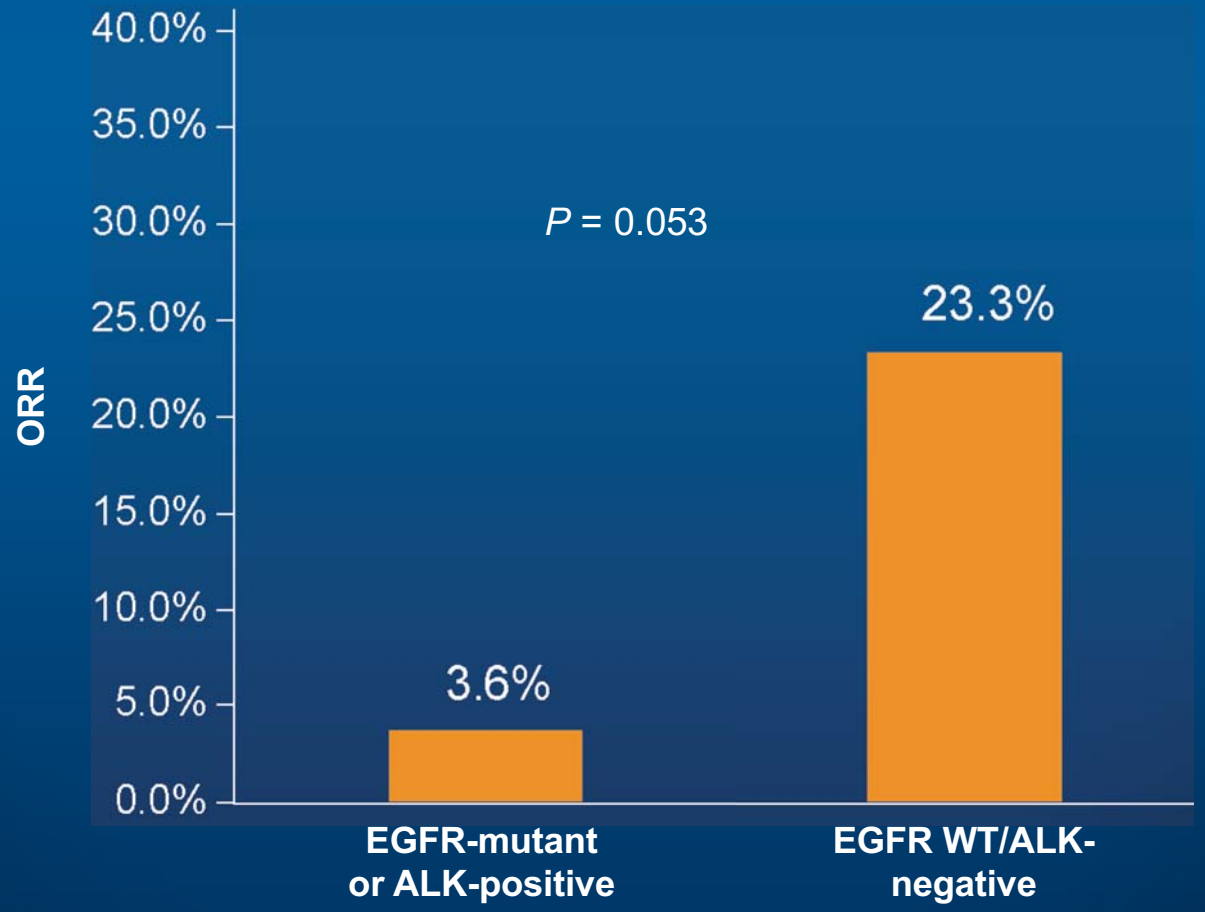
AURA3 Phase III Trial of Osimertinib versus Platinum Doublet in Locally Advanced or Metastatic EGFR T790M Mutation-Positive NSCLC



	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	10.1 (8.3-12.3)	0.30 (0.23-0.41) $p < 0.001$
Platinum-pemetrexed	4.4 (4.2-5.6)	

Mok TS et al. *N Engl J Med* 2017;376(7):629-40.

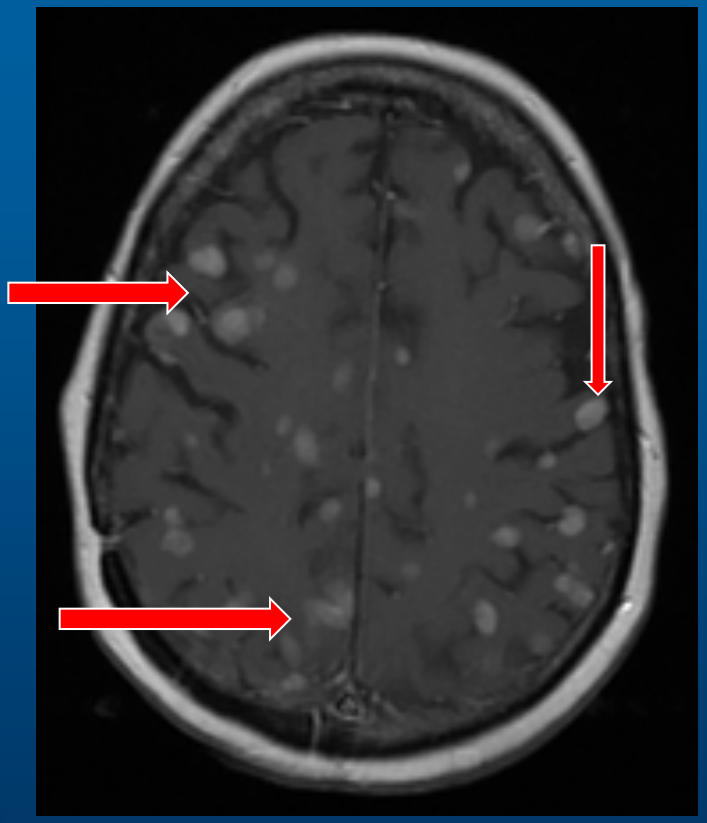
Association between Response Rates to PD-1 Pathway Blockade and EGFR and ALK Status in NSCLC



Gainor JF et al. *Clin Cancer Res* 2016;22(18):4585-93.

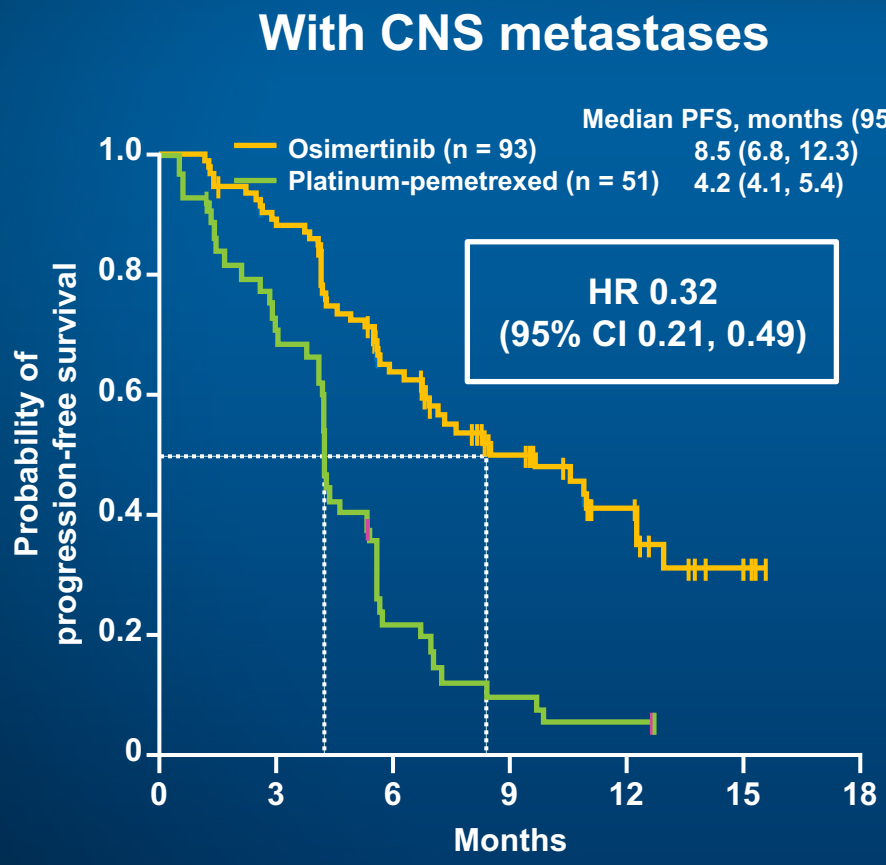
Key Considerations

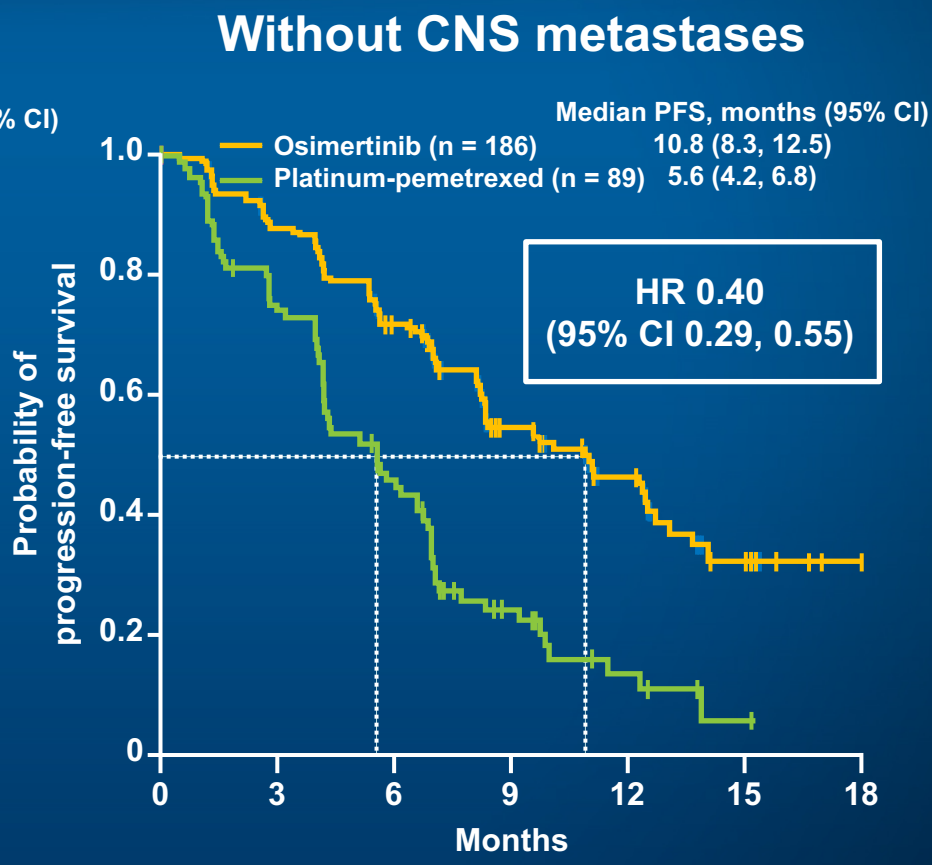
- TKIs for patients with brain metastases



A patient with lung cancer and bilateral brain metastases, image courtesy of Kelly EH Goodwin, MSN, RN, ANP-BC

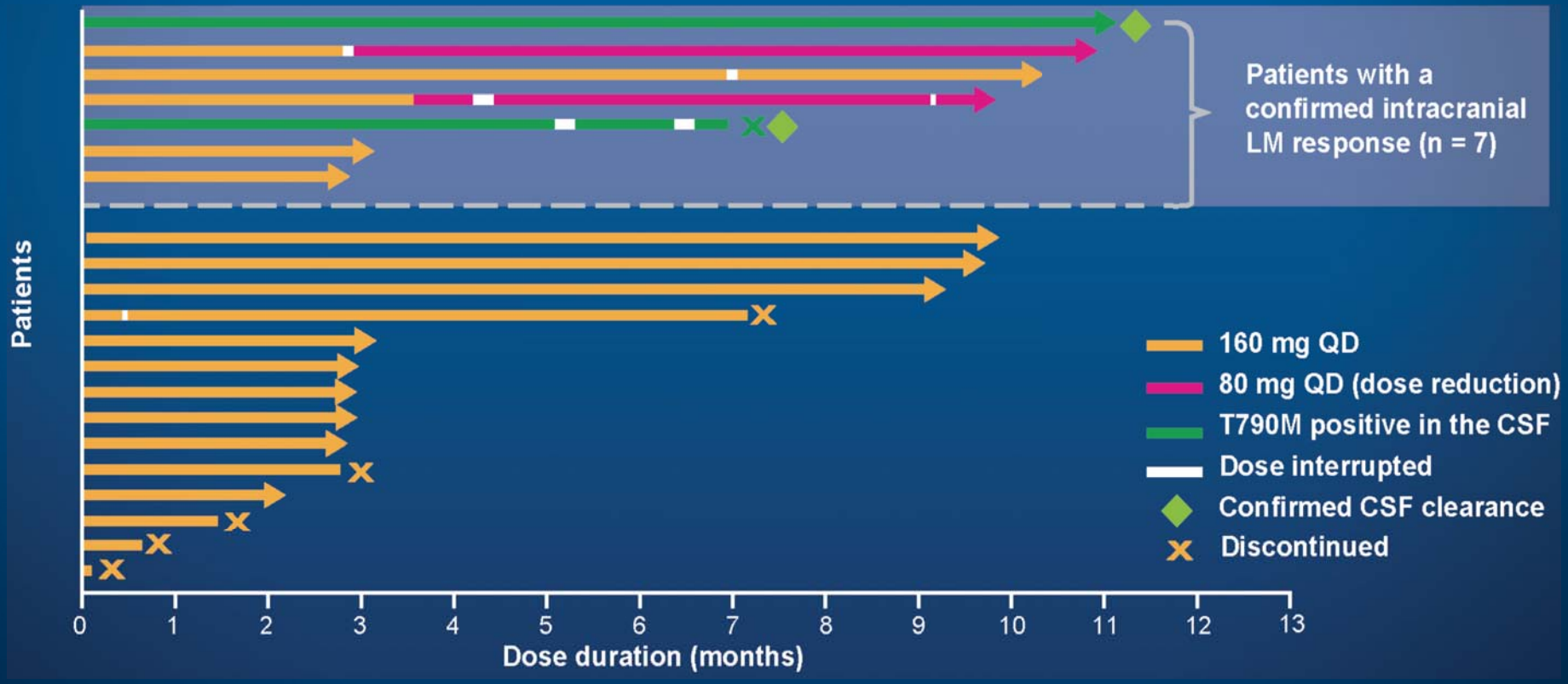
AURA3: PFS Benefit with Osimertinib in Patients with CNS Metastases at Baseline





Mok TS et al. *N Engl J Med* 2017;376(7):629-40.

BLOOM: Time on Treatment with Osimertinib for Patients with Leptomeningeal Carcinomatosis

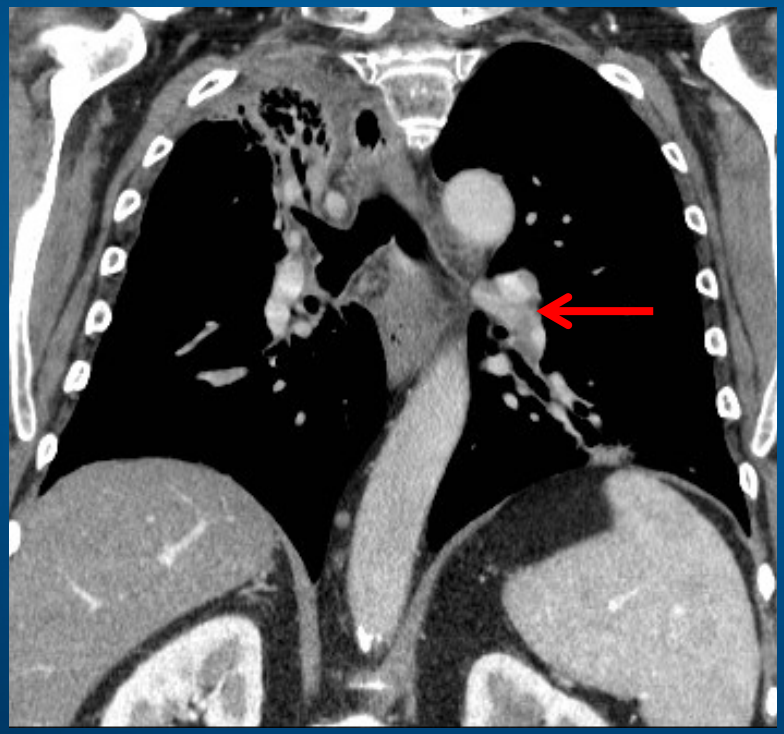


Yang JC et al. *Proc ASCO* 2016;Abstract 9002.

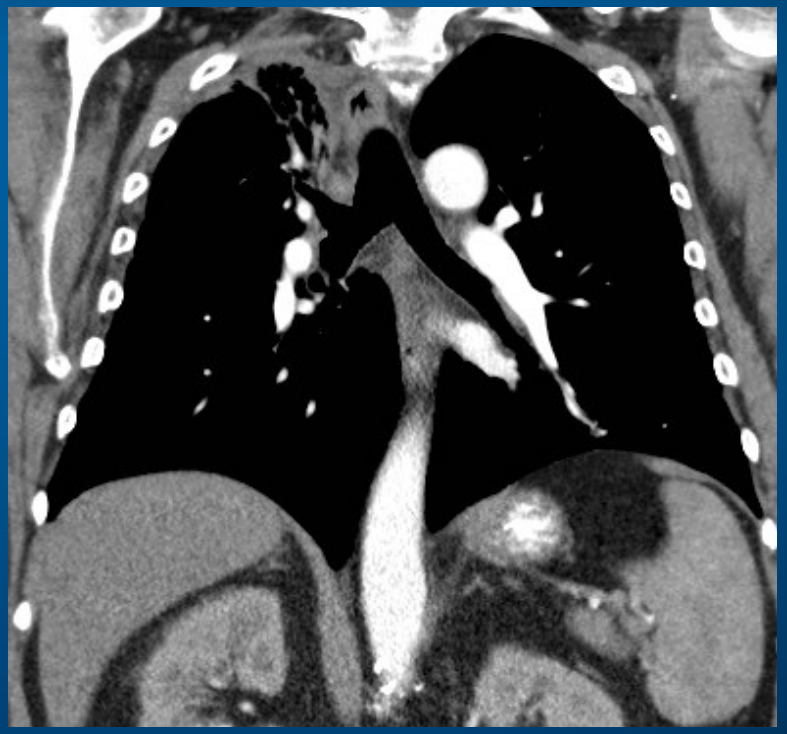
71-Year-Old Woman, Never Smoker with EGFR T790M Mutation-Positive Metastatic NSCLC (Ms Goodwin)

- April 2008: DCIS in the left breast and concurrent Stage IIIA lung adenocarcinoma
  - L breast lumpectomy, RUL lobectomy, RLL superior segmentectomy
  - EGFR L858R mutation identified
  - Adjuvant cisplatin/docetaxel followed by mediastinal RT
- 12/2009: New bilateral pulmonary nodules, brain metastasis
  - SRS to brain
  - Erlotinib (2/2010 – 1/2014)
- Disease progression in chest
  - Thoracentesis fluid reveals T790M
- Sought alternative therapy in Mexico

71-Year-Old Woman, Never Smoker with EGFR T790M Mutation-Positive Metastatic NSCLC (Ms Goodwin)



9/18/2015 baseline

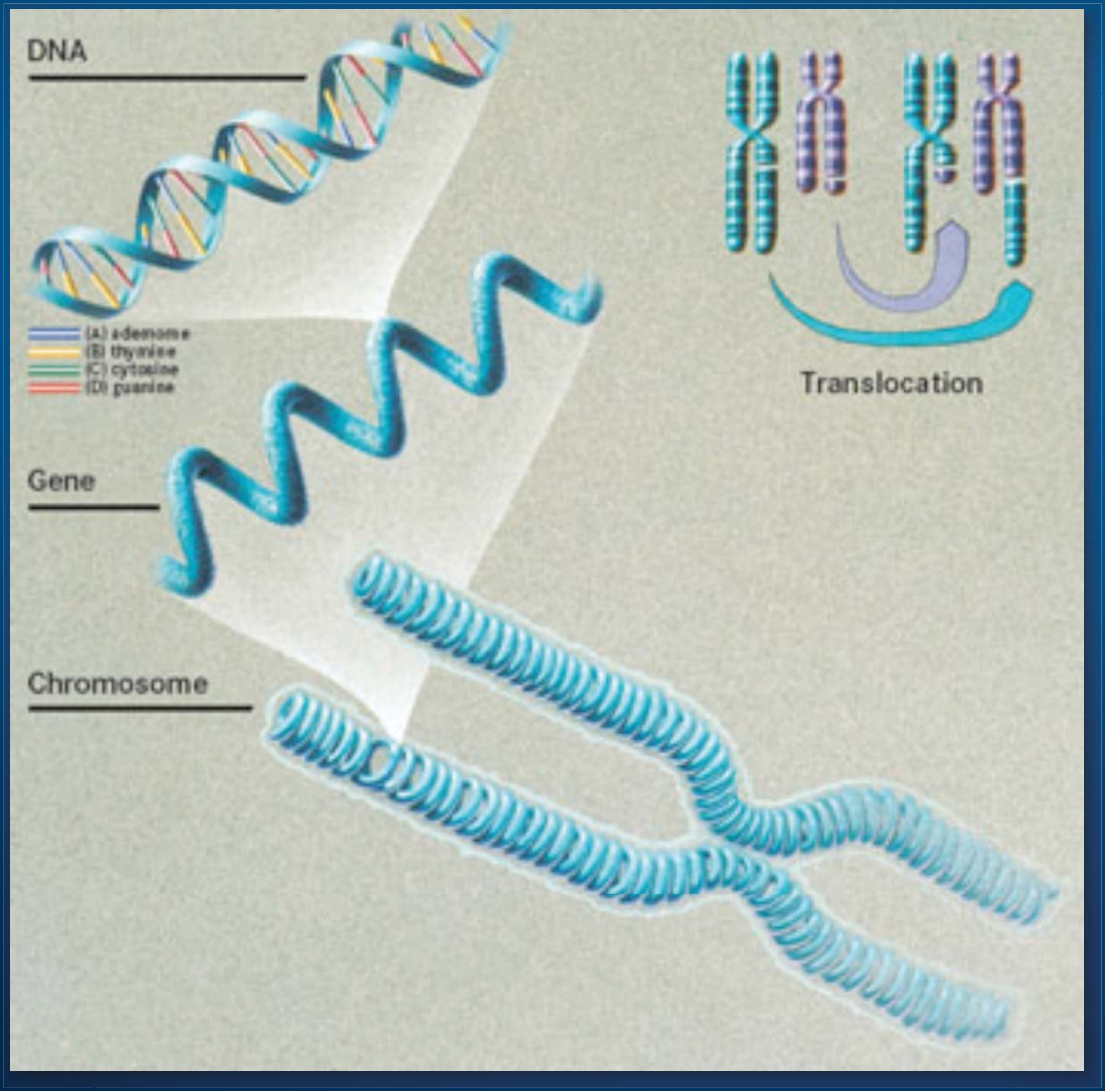


11/6/15 first restaging
on osimertinib

Module 5:
ALK-Mutant Metastatic NSCLC


Early-Stage NSCLC
Locally Advanced NSCLC
EGFR-Mutant Metastatic NSCLC
ALK-Mutant Metastatic NSCLC
Other Targetable Mutations in Metastatic NSCLC
Pan-Wild-Type Nonsquamous Metastatic NSCLC
Pan-Wild-Type Squamous Metastatic NSCLC

Anaplastic Lymphoma Kinase (ALK) Rearrangement in Cancer

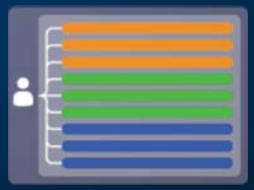


- Chromosomal translocation: Most common ALK abnormality in cancer
- Rearrangement of genetic info: Parts of one chromosome break off and fuse with another or flip around (inversion)
- Result: New gene and expression of **fusion protein**

Cancer Genome Atlas, National Cancer Institute

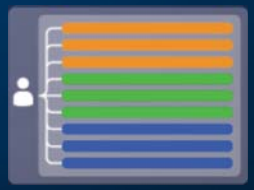
Key Considerations

- TKI versus chemotherapy
- Efficacy tolerability and selection of TKI (crizotinib, ceritinib, alectinib, brigatinib)
- Brain metastases



FDA-Approved ALK Inhibitors

- **Crizotinib**
  - Metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test
  - Tolerability issues: Hypogonadism, visual disturbance, gastrointestinal (GI) toxicities
- **Ceritinib**
  - Progressed on or are intolerant to crizotinib
  - Tolerability issues: GI toxicities
- **Alectinib**
  - Progressed on or are intolerant to crizotinib
  - Tolerability issues: Neutropenia
- **Brigatinib**
  - Progressed on or are intolerant to crizotinib
  - Tolerability issues: Pneumonitis, pneumonia, GI toxicities



ALK Inhibitors: Comparison of Activity

	Crizotinib	Ceritinib	Alectinib	Brigatinib
Indication	ALK+ NSCLC	ALK resistance	ALK resistance	ALK resistance
Highly active	Yes	Yes	Yes	Yes
Tolerability	Good	Moderate	Good	Good
CNS activity	Some	Good	Good	Good
Potency against resistance	Poor	Moderate	Moderate	Good

Courtesy of Geoffrey R Oxnard, MD

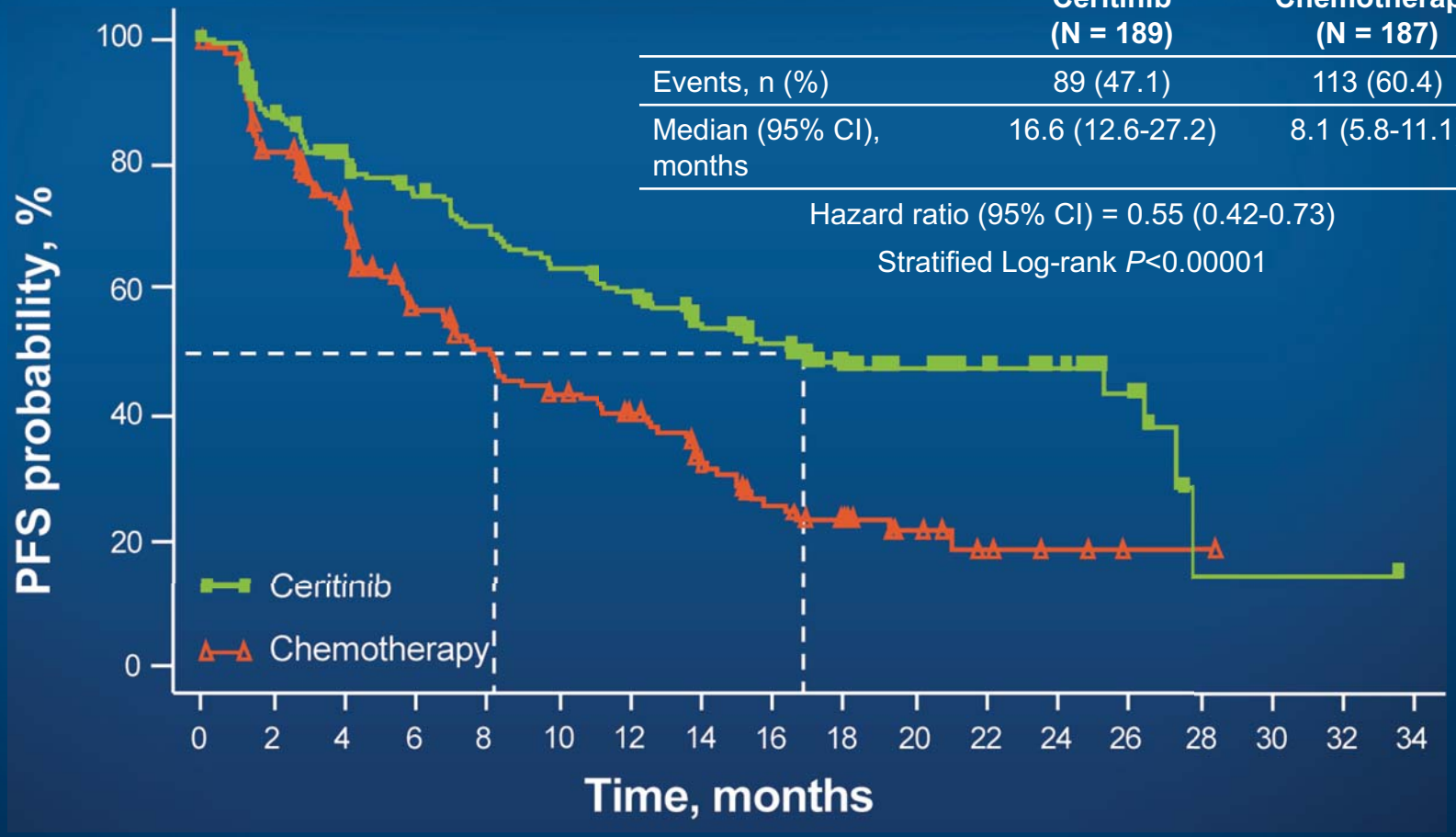
Kwak et al. *N Engl J Med* 2010; Awad et al. *Clin Adv Hematol Oncol* 2014; Kodama et al. *Mol Cancer Ther* 2014; Solomon et al. *J Clin Oncol* 2016.

ASCEND-4: First-Line Ceritinib versus Platinum-Based Chemotherapy in Advanced NSCLC

	Ceritinib (N = 189)	Chemotherapy (N = 187)
Events, n (%)	89 (47.1)	113 (60.4)
Median (95% CI), months	16.6 (12.6-27.2)	8.1 (5.8-11.1)

Hazard ratio (95% CI) = 0.55 (0.42-0.73)

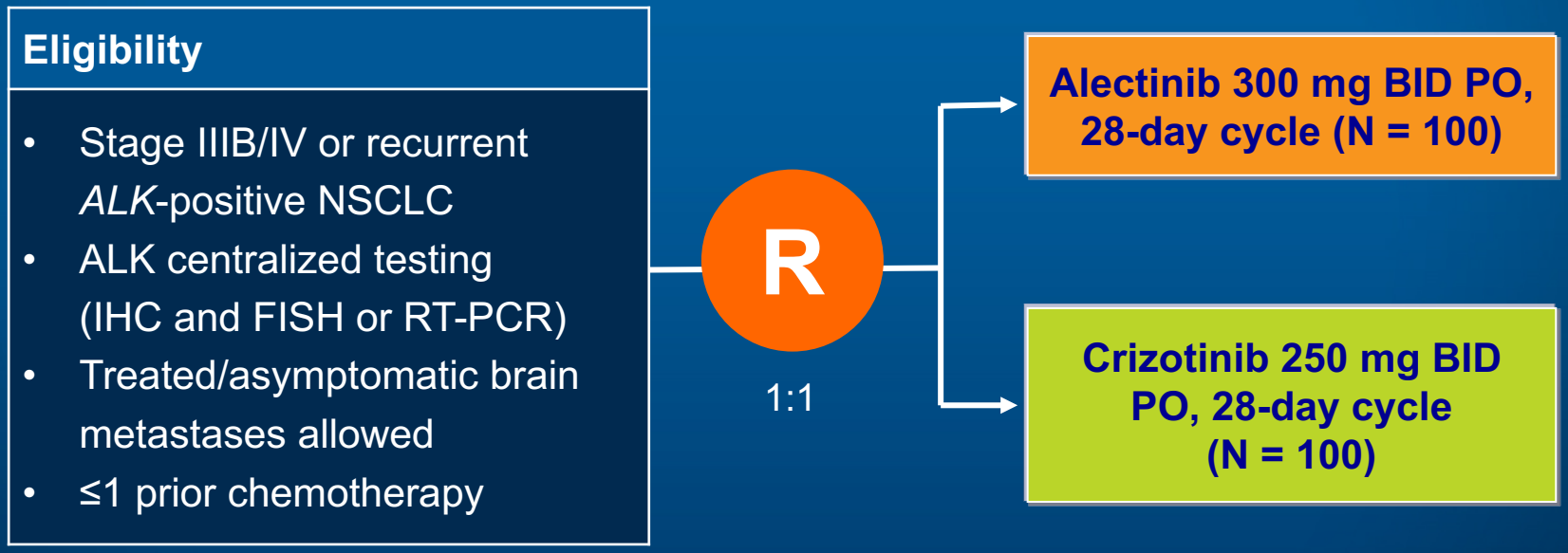
Stratified Log-rank *P*<0.00001



Ceritinib demonstrated an estimated 45% risk reduction vs chemotherapy

Soria J-C et al. *Lancet* 2017;39(10072):917-29.

J-ALEX: A Phase III Study Comparing Alectinib to Crizotinib in Japanese TKI-Naïve Patients

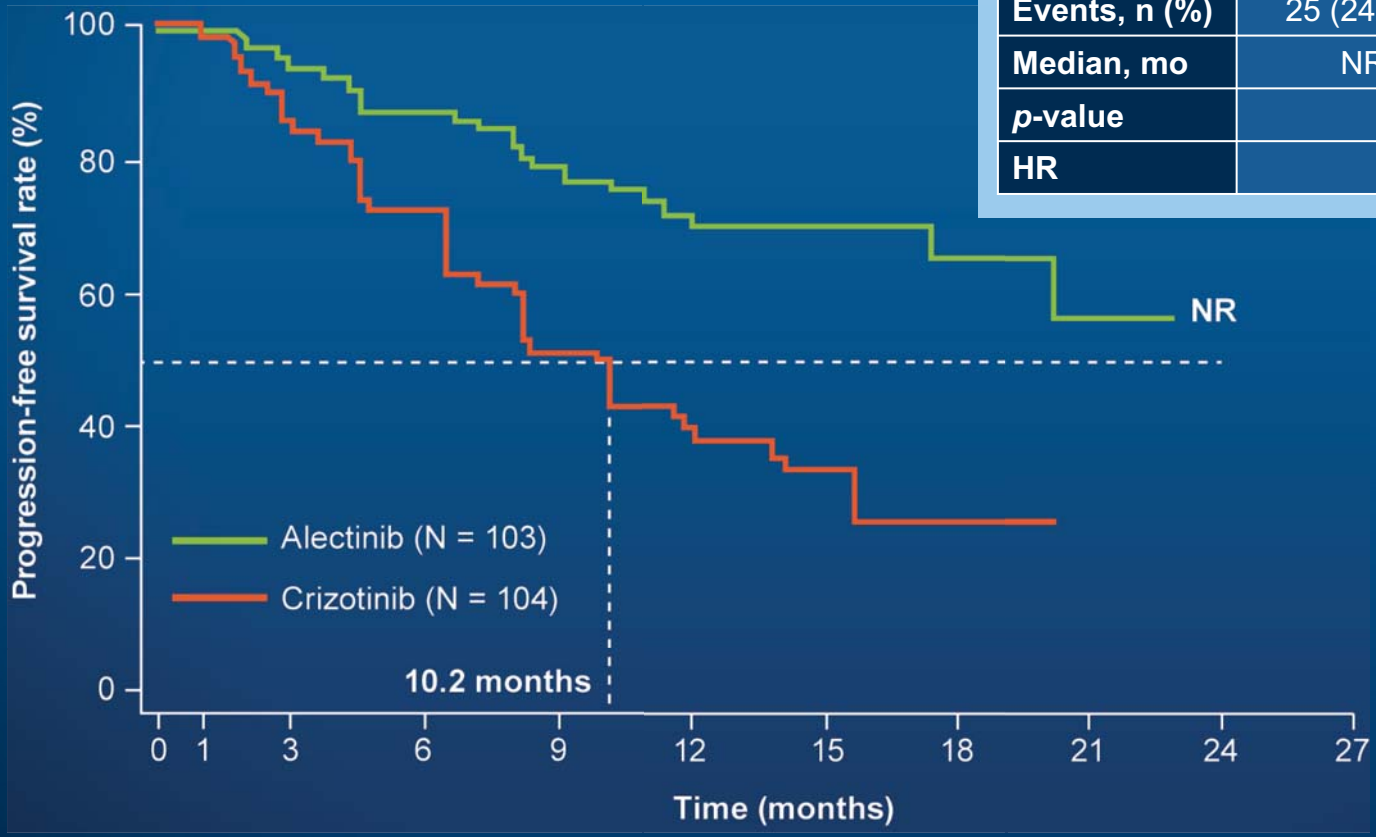


Primary endpoint: PFS assessed by independent review facility

Nokihara H et al. *Proc ASCO* 2016;Abstract 9008.

J-ALEX Study: Progression-Free Survival (ITT)

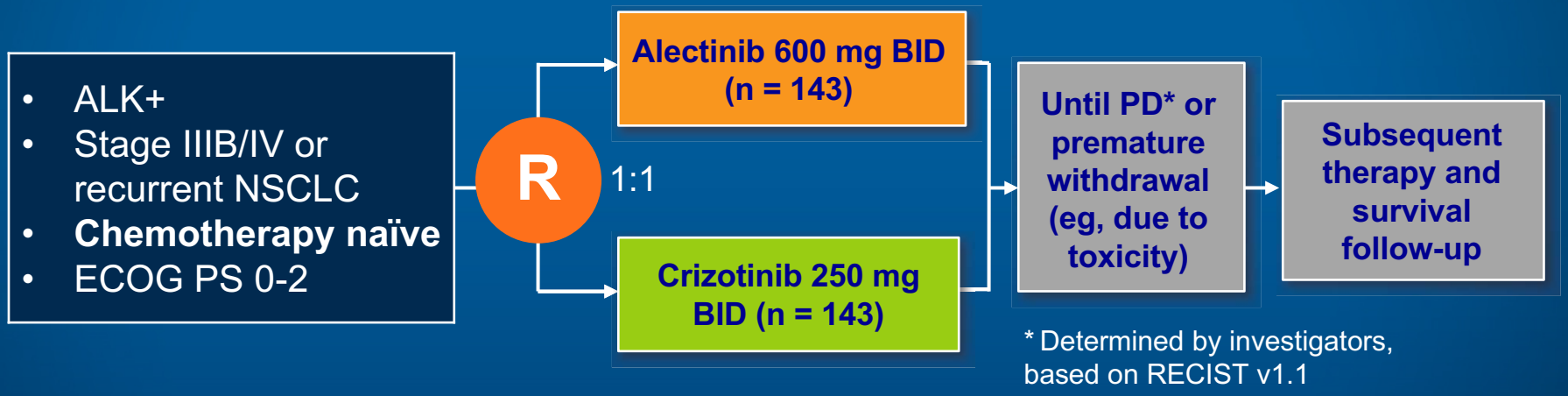
	Alectinib	Crizotinib
Events, n (%)	25 (24.3%)	58 (55.8%)
Median, mo	NR	10.2
***p*-value**	<0.0001	
HR	0.34	



- Consistent benefit observed with alectinib in all subgroups
- Patients with brain metastases: HR 0.08 favoring alectinib

Nokihara H et al. *Proc ASCO* 2016;Abstract 9008.

ALEX Phase III Trial Design



In comparison to crizotinib, alectinib demonstrated a statistically significant improvement in PFS in the Japanese Phase III parallel trial J-ALEX (HR = 0.34, $p < 0.0001$).

Ou SHI et al. *Proc ASCO* 2015;Abstract 8008; Nokihara H et al. *Proc ASCO* 2016;Abstract 9008.

ALEX Phase III Trial Meets Its Primary Endpoint

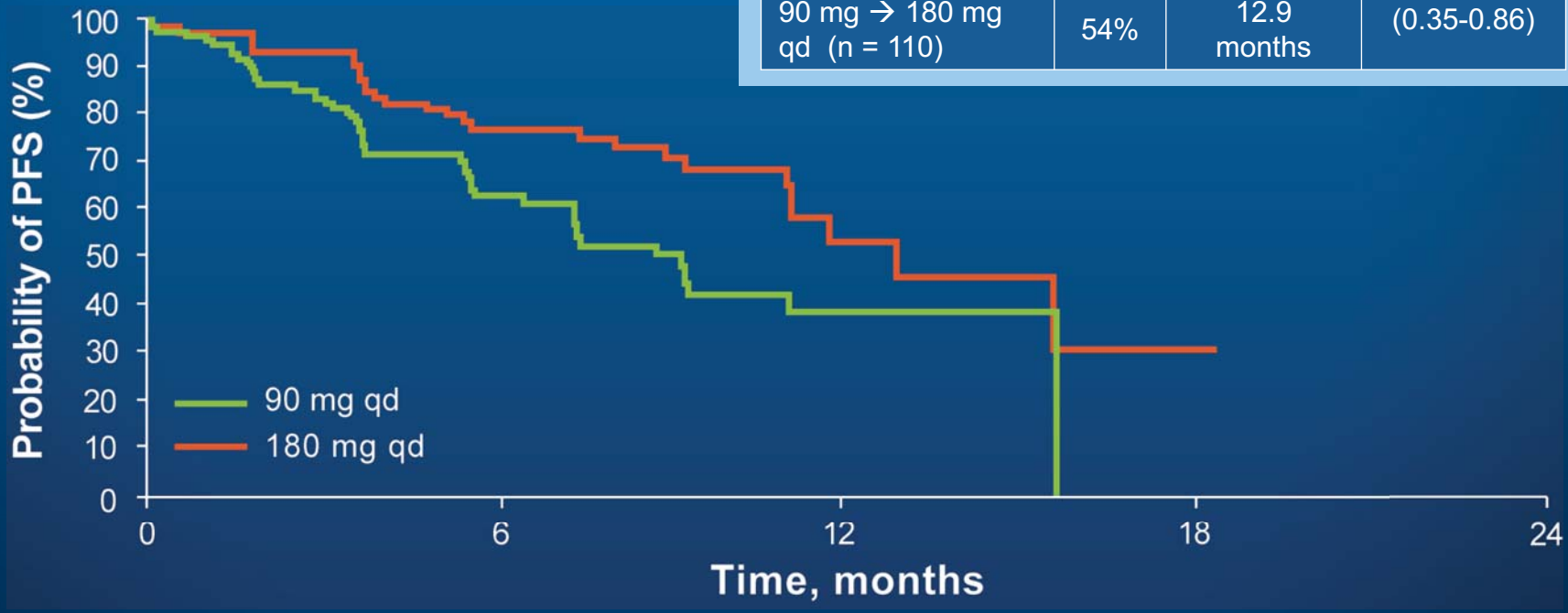
April 10, 2017 - The global, randomized phase III ALEX study met its primary endpoint and showed that alectinib as an initial (first-line) treatment significantly reduced the risk of disease worsening or death (progression-free survival, PFS) compared to crizotinib in people with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). The safety profile of alectinib was consistent with that observed in previous studies, with no new or unexpected adverse events.

Primary results of the ALEX trial will be presented at ASCO 2017 on Tuesday, June 6th at 12:09 pm ET

http://www.roche.com/media/store/releases/med-cor-2017-04-10.htm; https://iplanner.asco.org/am2017/#/

ALTA: A Phase II Trial of Brigatinib in Crizotinib-Refractory ALK-Rearranged NSCLC

	ORR	Median PFS	PFS HR
90 mg qd (n = 112)	45%	9.2 months	0.55 (0.35-0.86)
90 mg → 180 mg qd (n = 110)	54%	12.9 months	



Broad activity against a range of resistance mutations

Kim D-W et al. *Proc ASCO* 2016;Abstract 9007.

ALTA: Select Adverse Events

Any grade AE (≥10% of patients)	Brigatinib 90 mg qd (n = 109)	Brigatinib 180 mg qd (n = 110)
Nausea	33%	40%
Diarrhea	19%	38%
Cough	18%	34%
Dyspnea	21%	21%
Hypertension	11%	21%

A subset of pulmonary AEs with early onset (including dyspnea, hypoxia, cough, pneumonia, pneumonitis) occurred in 14 (6%) patients, before dose escalation to 180 mg

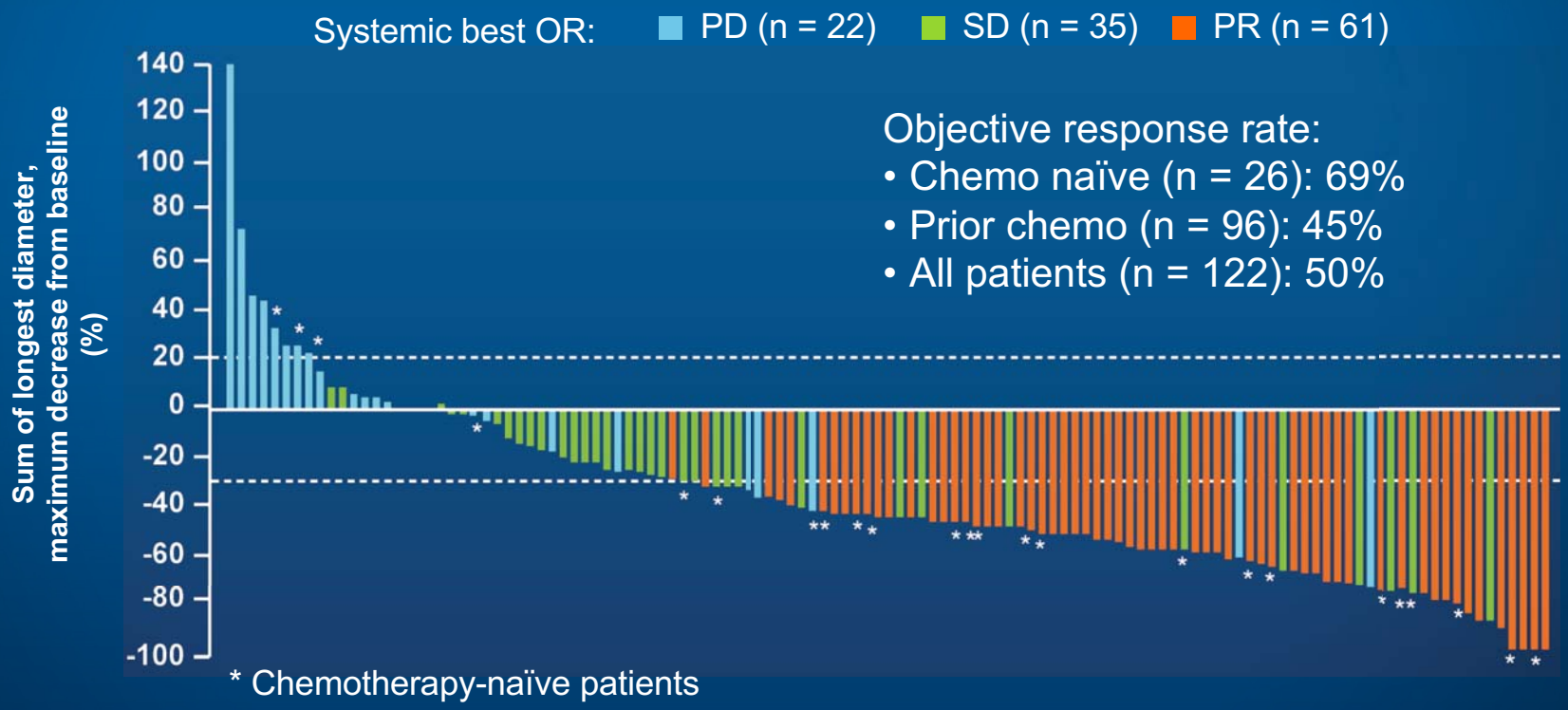
Kim D-W et al. *Proc ASCO* 2016;Abstract 9007.

Brigatinib Received Accelerated FDA Approval for ALK Mutation-Positive NSCLC

April 28, 2017 – Brigatinib has received Accelerated Approval from the US Food and Drug Administration (FDA) for the treatment of patients with anaplastic lymphoma kinase-positive (ALK+) metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under Accelerated Approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

https://www.takeda.com/newsroom/newsreleases/2017/alunbrig-fda-approval/

Phase II Study: Activity of Alectinib in Patients with Crizotinib-Resistant ALK-Positive NSCLC



Ou SHI et al. *J Clin Oncol* 2016;34(7):661-8.

29-Year-Old Medical Student, Never Smoker with ALK-Rearranged, Metastatic NSCLC (Ms Reed)

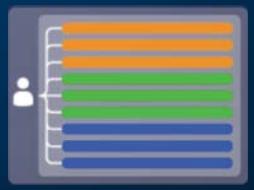
- Fall 2011: Urgently admitted for presumed pneumonia
  - Mediastinal mass with adenopathy, biopsy-proven adenocarcinoma
- 9/2011: Initiated cisplatin/pemetrexed
  - Pathology returned: EML4, ALK2, p23 translocated mutation
- 9/11/2011 – 5/11/2012: Crizotinib, with PD
- 5/30 – 11/18/2012: Clinical trial of ceritinib, with PD
- 12/12/12 – 3/2013: Cisplatin/pemetrexed/bevacizumab, with CR
  - 3/2013 – 4/2014: Maintenance pemetrexed/bevacizumab
- 5/2014: Cisplatin/pemetrexed + RT to neck and axilla
- 6/27/2014 – 3/06/2015: Continued pemetrexed with addition of crizotinib
- 4/15/2015: LUN 257 clinical trial with lorlatinib

Module 6:
Other Targetable Mutations in Metastatic NSCLC

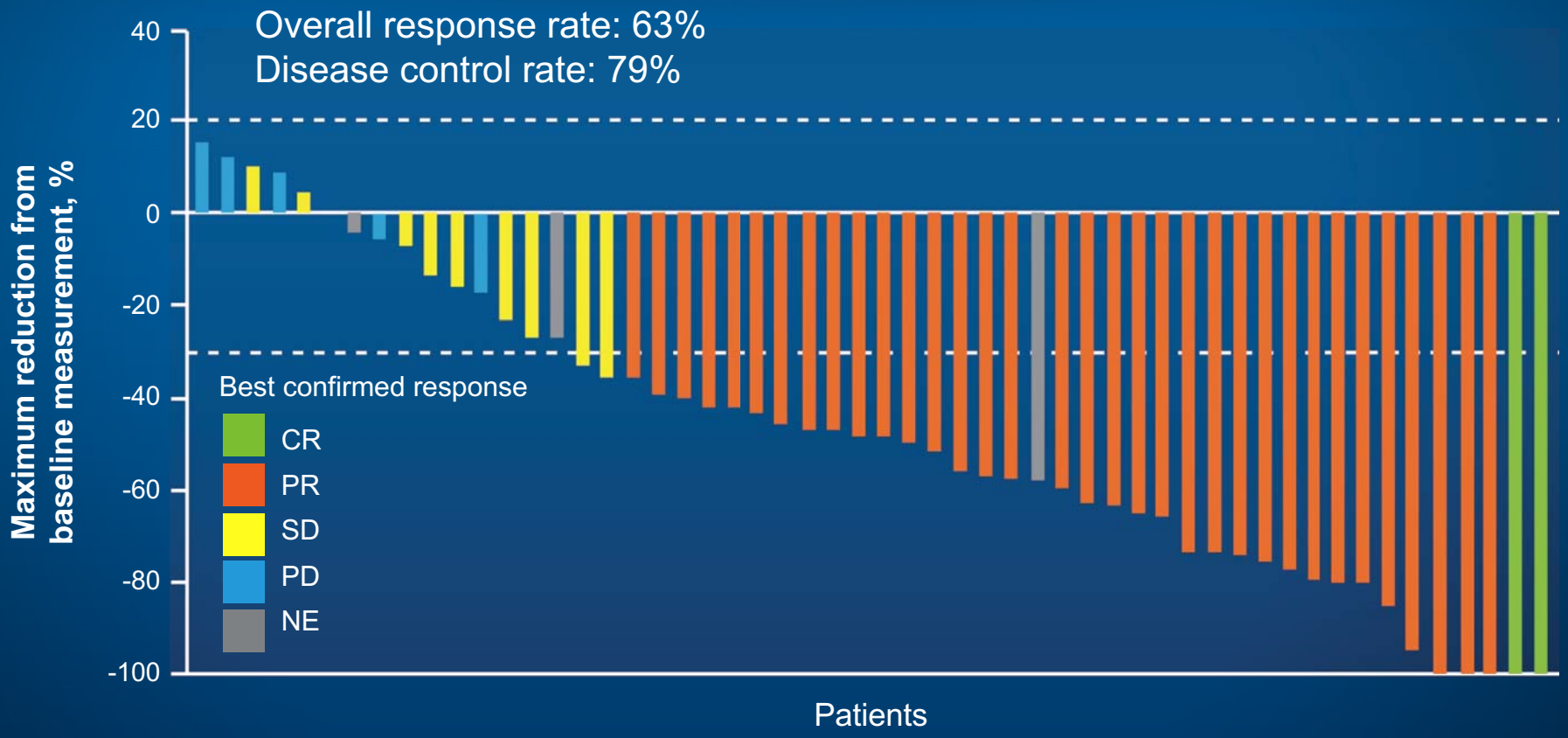

Early-Stage NSCLC
Locally Advanced NSCLC
EGFR-Mutant Metastatic NSCLC
ALK-Mutant Metastatic NSCLC
Other Targetable Mutations in Metastatic NSCLC
Pan-Wild-Type Nonsquamous Metastatic NSCLC
Pan-Wild-Type Squamous Metastatic NSCLC

Key Considerations

- Types of mutation and response to BRAF inhibitors alone or with MEK inhibitor
- Tolerability profile of combined BRAF and MEK inhibition



Dabrafenib and Trametinib in BRAF V600E-Mutant Metastatic NSCLC



NE patients did not have a follow-up scan required for confirmation.

Planchard D et al. *Lancet Oncol* 2016;17:984-93.

Dabrafenib/Trametinib: Select Adverse Events

Adverse event	Grade 1-2	Grade ≥3
Pyrexia	44%	2%
Nausea	40%	0%
Vomiting	35%	0%
Diarrhea	32%	2%
Decreased appetite	30%	0%
Neutropenia	11%	9%
Hyponatremia	4%	7%
Anemia	12%	6%
Cutaneous squamous cell carcinoma*	0%	4%
Basal cell carcinoma*	2%	2%

Serious adverse events: 32/57 (56%)

* Cutaneous squamous cell carcinoma and basal cell carcinoma occurred in 12% and 5%, respectively, in a study of dabrafenib alone

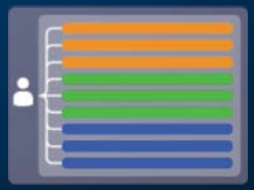
Planchard D et al. *Lancet Oncol* 2016;17:984-93. Planchard D et al. *Lancet Oncol* 2016;17:642-50.

Cost and reimbursement issues aside, what targeted therapy, if any, would you most likely recommend for a patient with metastatic NSCLC and a BRAF V600E tumor mutation? In which line of therapy, if any, would you most likely administer a BRAF inhibitor (with or without a MEK inhibitor)?

	TARGETED THERAPY	LINE OF TREATMENT
 RAMASWAMY GOVINDAN, MD	Dabrafenib with trametinib	First line
 JOEL W NEAL, MD, PHD	Dabrafenib and trametinib	First line
 GREGORY J RIELY, MD, PHD	Dabrafenib with trametinib	First line
 JULIE R BRAHMER, MD	Dabrafenib with trametinib	Second line
 COREY J LANGER, MD	Dabrafenib with trametinib	First line
 HEATHER WAKELEE, MD	Dabrafenib with trametinib	Second line

Key Considerations: Other Actionable Genomic Alterations

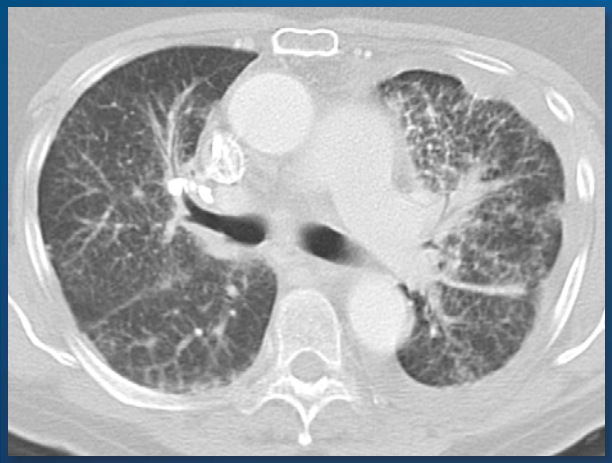
- **ROS1**
  - Crizotinib, ceritinib?
- **MET exon 14**
  - Crizotinib
- **RET**
  - Cabozantinib, vandetanib
- **HER2**
  - Trastuzumab, T-DM1, afatinib



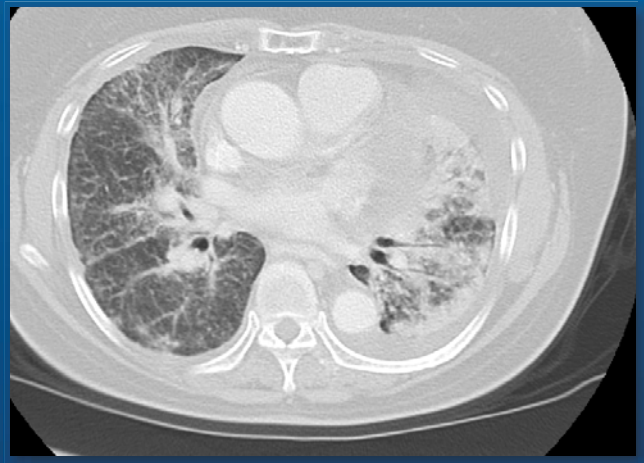
65-Year-Old Woman, Registered Nurse, Never Smoker and Jehovah's Witness with Metastatic BRAF-Mutant NSCLC (Ms Reed)

- Early 2014: Adenocarcinoma of the lung; hypermetabolic uptake in cervical and lumbar spine, supraclavicular and mediastinal regions
- 2/2014 – 7/2016: Clinical trial of carboplatin/pemetrexed +/- OGX-427
- 8/2016: Tissue sent to Foundation Medicine; inadequate specimen
- 9/2016: Palliative RT to spine; tissue testing of axillary mass showed BRAF mutation
- 10/2016: Clinical trial with IDO1 inhibitor + anti-PD-1 antibody
  - 12/2016: Pneumonitis?
- 1/2017: Initiated treatment with vemurafenib/cobimetinib
  - PR after 8 weeks of treatment

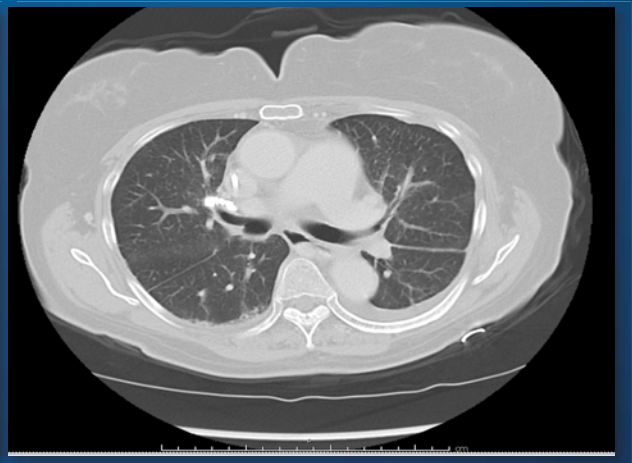
65-Year-Old Woman, Registered Nurse, Never Smoker and Jehovah's Witness with Metastatic BRAF-Mutant NSCLC (Ms Reed)



October 17, 2016
Baseline



December 27, 2016
IDO inhibitor + anti-PD-1 antibody



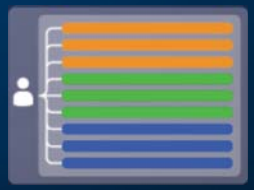
March 24, 2017
Vemurafenib + cobimetinib

Module 7:
Pan-Wild-Type Nonsquamous Metastatic NSCLC


Early-Stage NSCLC
Locally Advanced NSCLC
EGFR-Mutant Metastatic NSCLC
ALK-Mutant Metastatic NSCLC
Other Targetable Mutations in Metastatic NSCLC
Pan-Wild-Type Nonsquamous Metastatic NSCLC
Pan-Wild-Type Squamous Metastatic NSCLC

Key Considerations

- PD-L1 tissue levels
  - Choice of assays
- Chemotherapy versus CI as up-front treatment
  - Other CIs under development
- Potential new role for chemotherapy (carboplatin/pemetrexed) combined with CI
- Choice of chemotherapy with or without bevacizumab



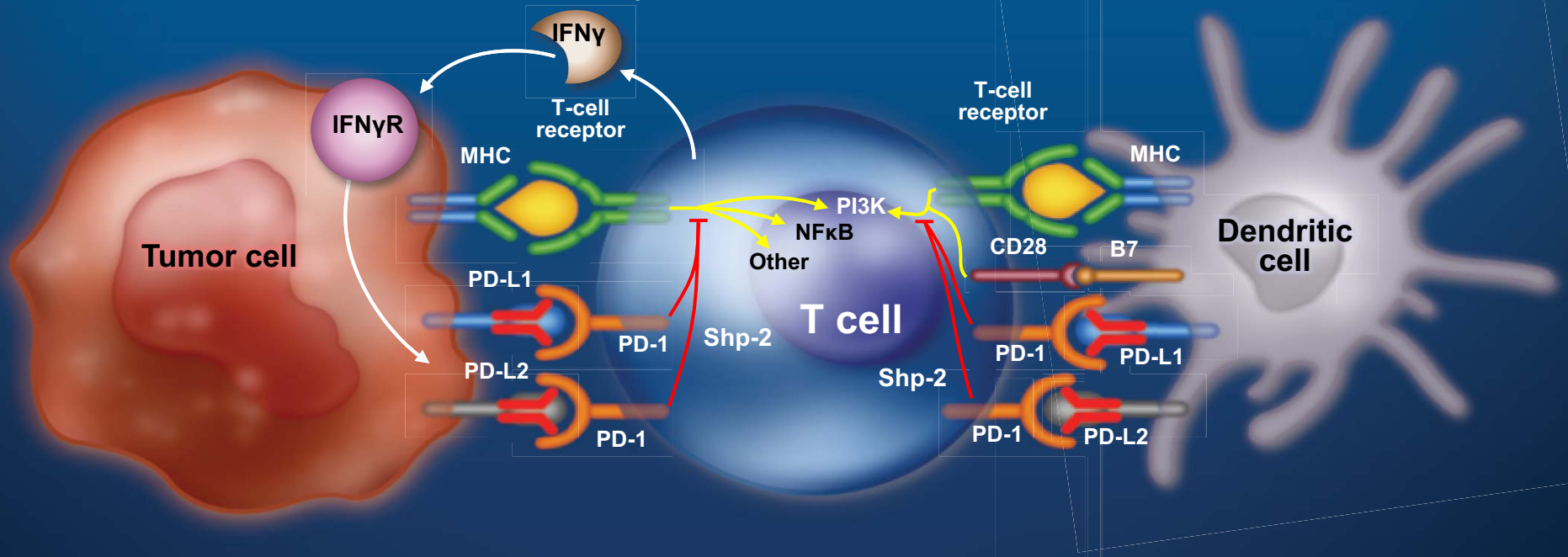
First-Line Chemotherapy Regimens for Metastatic Nonsquamous NSCLC

- Carboplatin/paclitaxel ± bevacizumab
  - Bevacizumab maintenance
  - Pemetrexed maintenance
- Carboplatin/pemetrexed ± bevacizumab
  - Bevacizumab maintenance
  - Pemetrexed maintenance
  - Pemetrexed/bevacizumab maintenance
- Other cisplatin- or carboplatin-based regimens combined with *nab* paclitaxel, pemetrexed, gemcitabine, docetaxel, etoposide or vinorelbine

NCCN NSCLC Guidelines, version 5. 2017

Anti-PD-1/PD-L1 Antibodies: Mechanism of Action

- PD-1 expression on tumor-infiltrating lymphocytes is associated with decreased cytokine production and effector function
- 3 approved drugs:
- Nivolumab/pembrolizumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function
- Atezolizumab binds PD-L1 receptors



Nivolumab/Pembrolizumab: PD-1 Receptor Blocking Ab
Atezolizumab: PD-L1 Receptor Blocking Ab

PD-1/PD-L1 Inhibitors in NSCLC

Checkpoint inhibitor	Antibody type	Stage	PD-L1 test
Anti-PD-1			
Nivolumab (BMS-936558)	IgG4	Approved 2nd line CheckMate 057/017	28-8 "complementary"
Pembrolizumab (MK-3475)	IgG4 (humanized)	1st line – PD-L1 ≥50% 2nd line – PD-L1 ≥1% Keynote 010/024	22C3 "companion"
Anti-PD-L1			
Atezolizumab (MPDL3280A)	IgG1 (engineered)	Approved 2nd line OAK, POPLAR, BIRCH, IMpower	SP142 "complementary"
Durvalumab (MEDI-4736)	IgG1	Phase III (ATLANTIC, PACIFIC, BR31, ARCTIC, MYSTIC, LUNG-MAP)	SP263
Avelumab (MSB0010718C)	IgG1	Phase III (JAVELIN)	

National Institutes of Health. Available at: http://clinicaltrials.gov

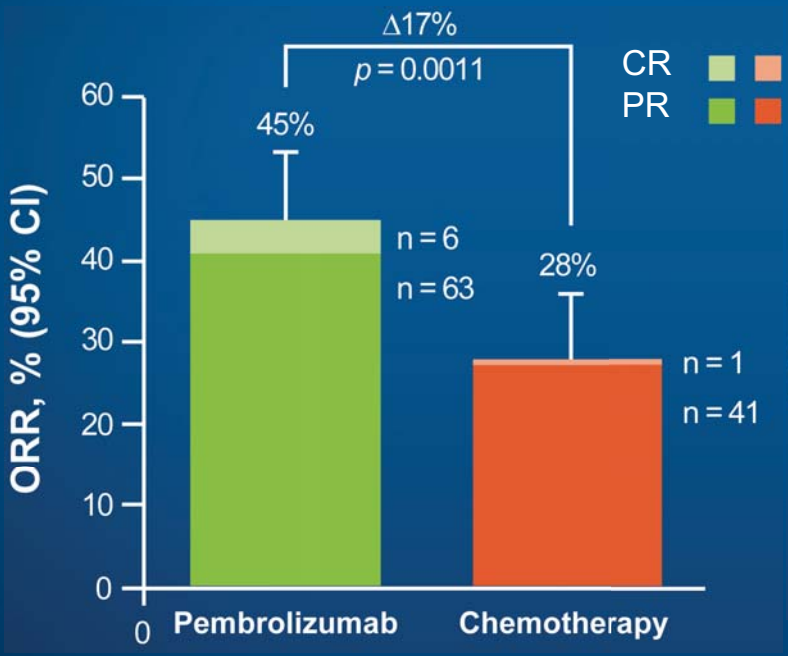
Results of Pivotal Second-Line PD-1/PD-L1 Inhibitor Studies in NSCLC

Anti-PD-1			
Study	**Randomization**	**Outcome**	**HR, *p*-value**
Checkmate 017 (squamous)	Nivo vs doce	mOS = 9.2 vs 6.0 mo	0.59, <0.001
Checkmate 057 (nonsquamous)	Nivo vs doce	mOS = 12.2 vs 9.4 mo	0.73, 0.0015
KEYNOTE-010	Pembro (2mg/kg) vs doce Pembro (10mg/kg) vs doce	mOS = 10.4 vs 8.5 mo mOS = 12.7 vs 8.5 mo	0.71, 0.0008 0.61, <0.0001
Anti-PD-L1			
OAK	Atezo vs doce	18-mo OS = 40% vs 27%	0.73, 0.0003

Brahmer J et al. *N Engl J Med* 2015;373(2):123-35; Borghaei H et al. *N Engl J Med* 2015;373(17):1627-39; Herbst RS et al. *Lancet* 2016;387(10027):1540-50; Rittmeyer A et al. *Lancet* 2017;389(10066):255-65.

KEYNOTE-024: A Phase III Trial of First-Line Pembrolizumab versus Chemotherapy in Advanced NSCLC

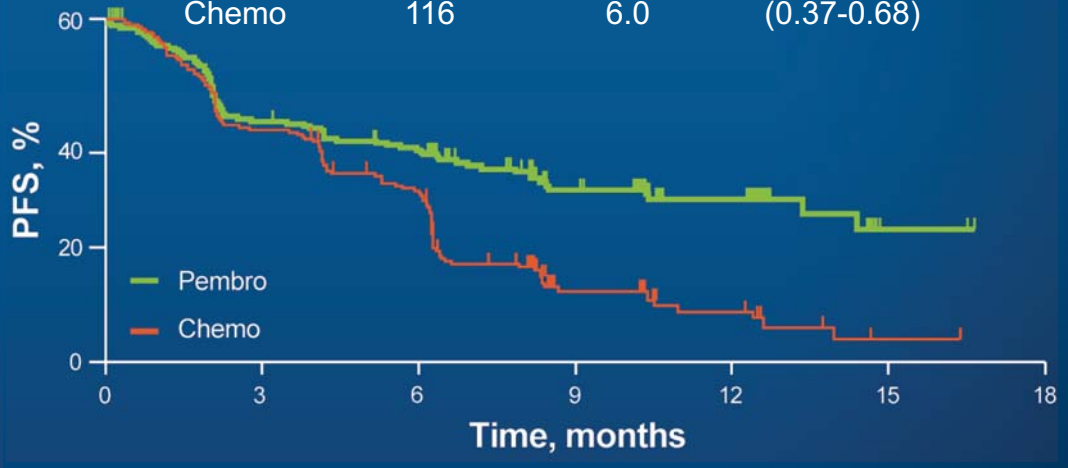
ORR



- **45% ORR is the best RR ever reported in 1st-line setting**
- Time to response is identical between pembrolizumab and chemotherapy

Progression-Free Survival

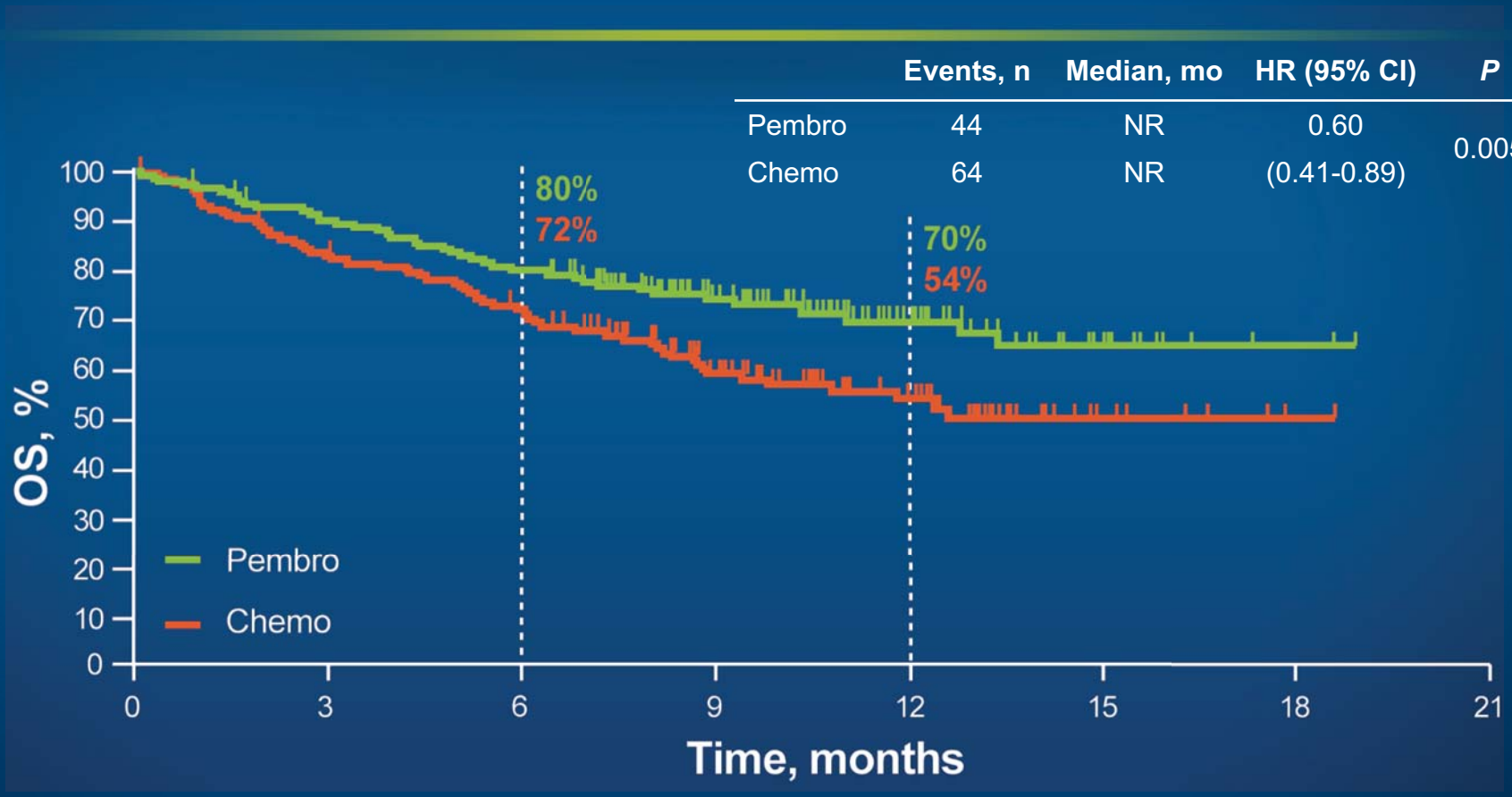
	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



- **PFS is improved by 4.3 months (HR of 0.50)**
- Improvement of PFS in all subgroups (except female/never smokers)
- **Strongest signal of PFS benefit observed in SCC** (HR of 0.35)

Reck M et al. *N Engl J Med* 2016;375(19):1823-33, *Proc ESMO* 2016;Abstract LBA8_PR.

KEYNOTE-024: Overall Survival

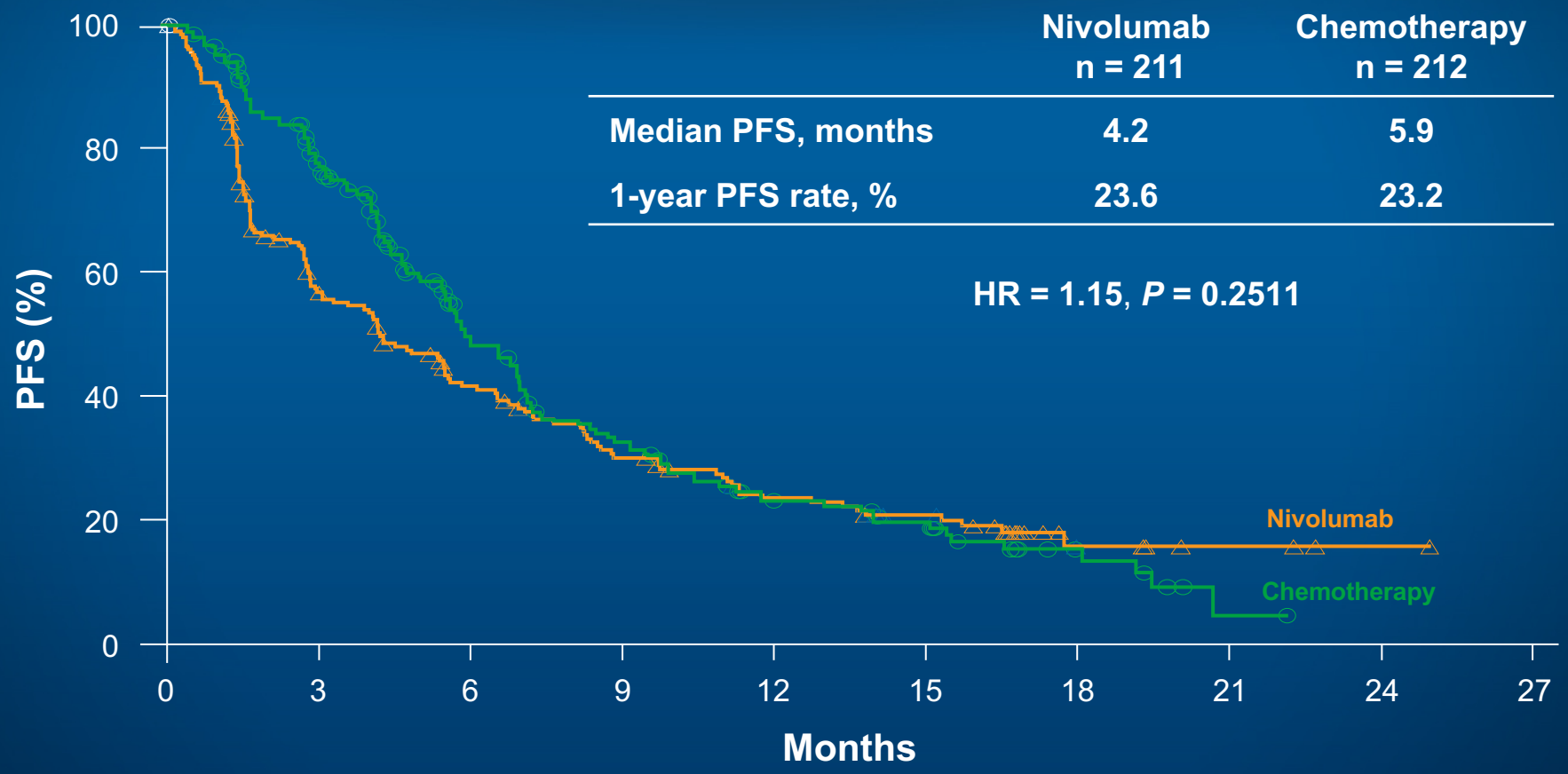


Clear survival benefit

- Estimated rate of OS at 12 months: 70% (pembro) vs 54% (chemo)
- HR for death: **0.60**
- Crossover **was limited to 50% of the patients**

Reck M et al. *N Engl J Med* 2016;375(19):1823-33; *Proc ESMO* 2016;Abstract LBA8_PR.

CheckMate 026: A Phase III Trial of First-Line Nivolumab versus Chemotherapy for PD-L1-Positive Metastatic/Recurrent NSCLC



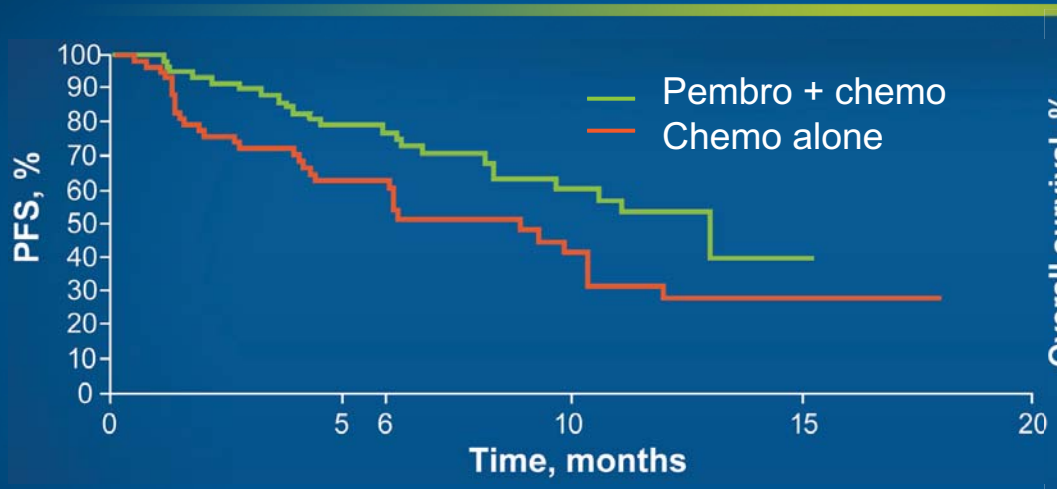
	Nivolumab n = 211	Chemotherapy n = 212
Median PFS, months	4.2	5.9
1-year PFS rate, %	23.6	23.2

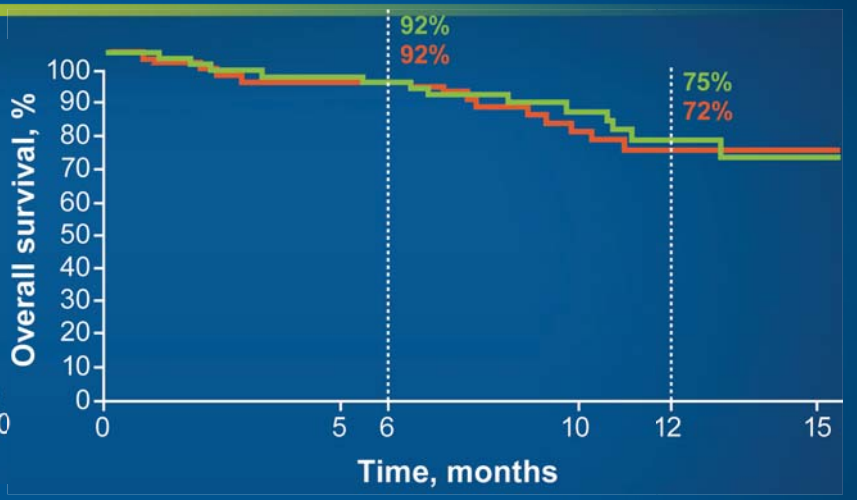
HR = 1.15, *P* = 0.2511

All randomized patients (≥1% PD-L1+): HR = 1.17

Socinski M et al. *Proc ESMO* 2016;Abstract LBA7_PR.

KEYNOTE-021: Carboplatin and Pemetrexed ± Pembrolizumab for Advanced Nonsquamous NSCLC





	Events, n	Median	HR (95% CI)
Pembro + chemo (n = 60)	23	13.0 mo	0.53 (0.31-0.91)
Chemo alone (n = 63)	33	8.9 mo	*p* = 0.0102

	Events, n	HR (95% CI)
Pembro + chemo	13	0.90 (0.42-0.91)
Chemo alone	14	

- **Median PFS improved by 4.1 months**
- No difference in OS
  - Estimated rate of OS @ 12 months: 75% (combo) vs 72% (CT)
- In chemotherapy arm, crossover is 51% to anti-PD-1/PD-L1 therapies (pembrolizumab and others)

Langer C et al. *Lancet Oncol* 2016;17(11):1497-508, *Proc ESMO* 2016;Abstract LBA46_PR.

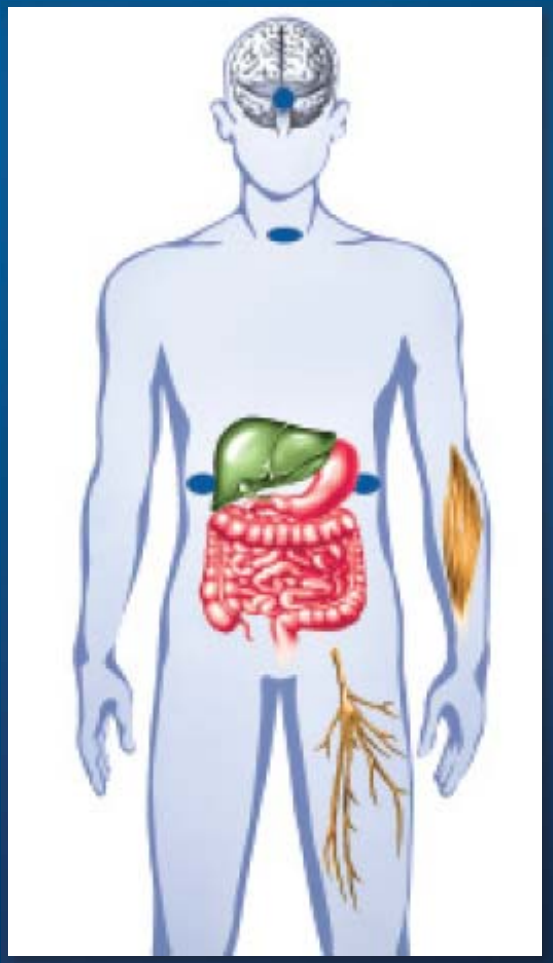
Key Considerations

- Spectrum of autoimmune toxicities of CIs
- CIs in patients with preexisting autoimmune considerations (Crohn's disease, psoriasis, SLE, multiple sclerosis)

Immune-Related Adverse Events (IRAEs) Associated with Immune Checkpoint Inhibitors

Occasional (5%-20%) irAEs
Grade 3/4 uncommon

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis
- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor and sensory neuropathies
- Arthritis

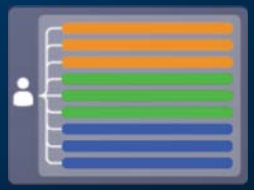


Less common: hematologic; cardiovascular; ocular; renal

Courtesy of Julie R Brahmer, MD

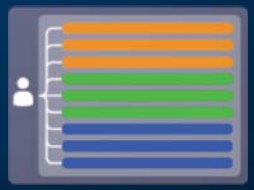
Key Considerations

- Second-line treatment for patients initially receiving chemotherapy
- Progression on a checkpoint inhibitor
- Role of maintenance treatment
- Ramucirumab with chemotherapy



Second-Line Therapy Options for Patients with Nonsquamous NSCLC and No Actionable Mutations

- Other chemotherapies
- Docetaxel + ramucirumab
- Pembrolizumab
- Nivolumab
- Atezolizumab



Ramucirumab

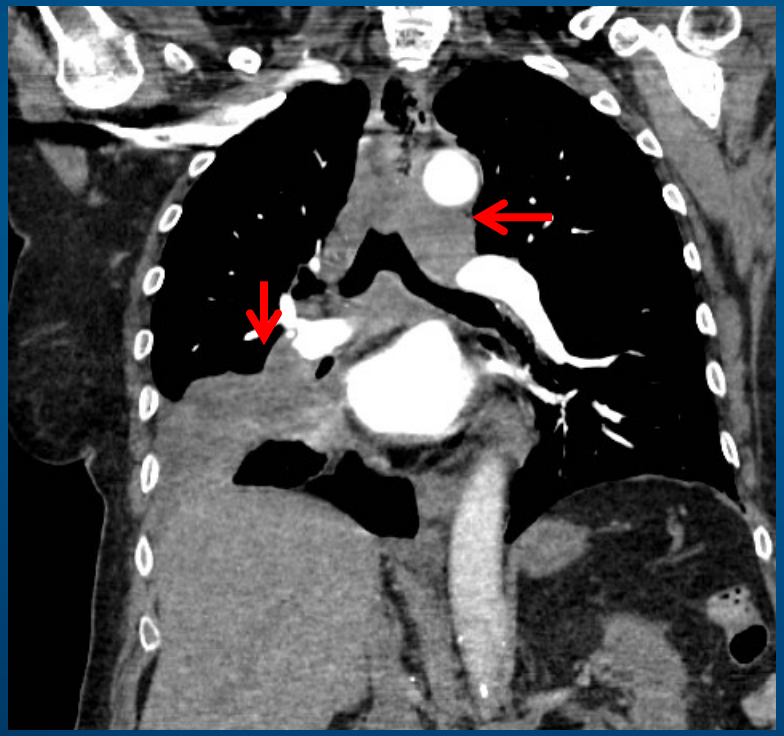
- A fully human monoclonal antibody against VEGFR-2
- Phase III REVEL study demonstrated survival advantage with ramucirumab and docetaxel versus docetaxel alone as 2nd-line therapy in metastatic NSCLC (nonsquamous and squamous)
  - Median OS: 10.5 vs 9.1 mo, HR = 0.86
  - Median PFS: 4.5 vs 3.0 mo, HR = 0.76
- More Grade 3/4 neutropenia, febrile neutropenia
- Approved as in the REVEL study setting and population

Garon EB et al. *Lancet* 2014;384(9944):665-73. Ramucirumab package insert, April 2017

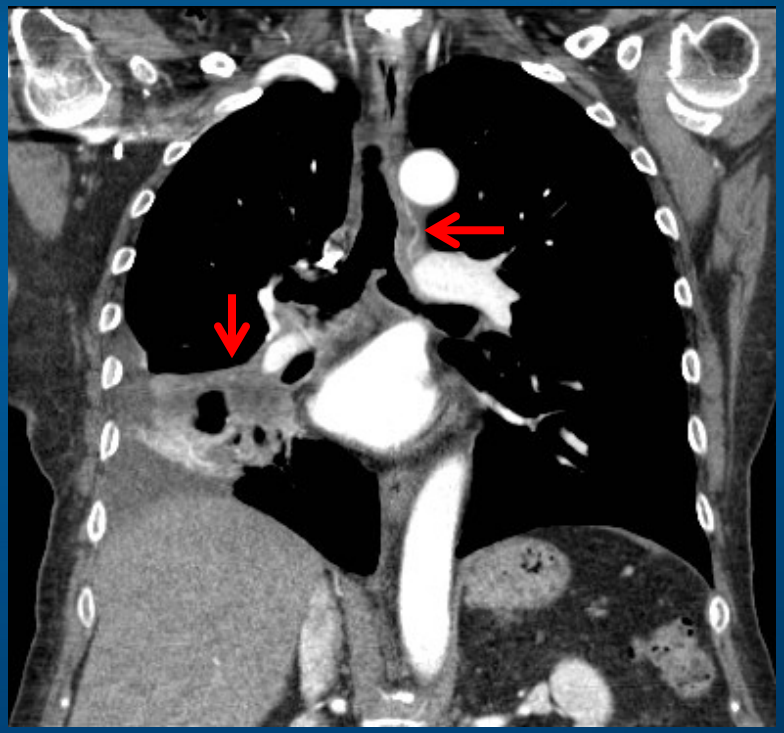
71-Year-Old Woman, Former Smoker with Metastatic NSCLC and PD-L1 Positivity >50% (Ms Goodwin)

- Summer 2016: Presents to PCP with significant PMH, comorbidities and dementia with apparent bronchitis
- Diagnosed with Stage IIIB NSCLC, admitted with hemoptysis
  - No response to palliative RT
  - Significant concerns re: chemo due to poor PS, recurrent infections
  - Worsening fatigue, weight loss and new dysphagia
- Molecular testing revealed PD-L1 positivity >50%
- 12/2016: Pembrolizumab initiated
  - Improvement in scans, symptoms and functional status
- Development of diarrhea raises concern for autoimmune colitis
  - Pembrolizumab held pending stool studies

71-Year-Old Woman, Former Smoker with Metastatic NSCLC and PD-L1 Positivity >50% (Ms Goodwin)



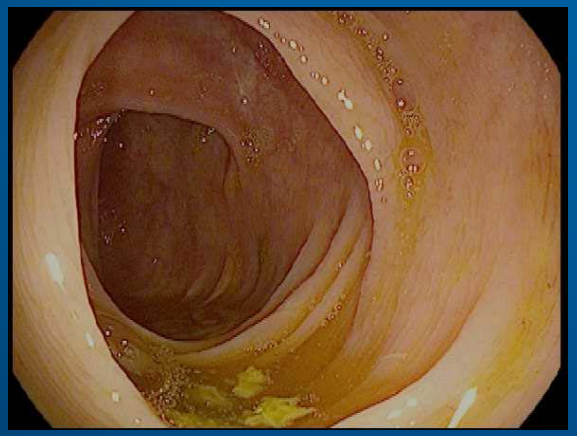
11.21.16 baseline

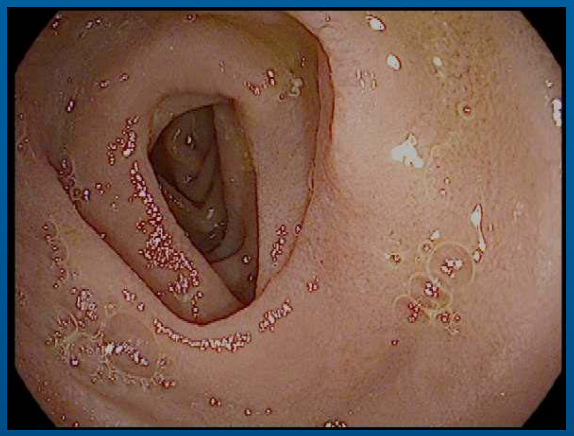


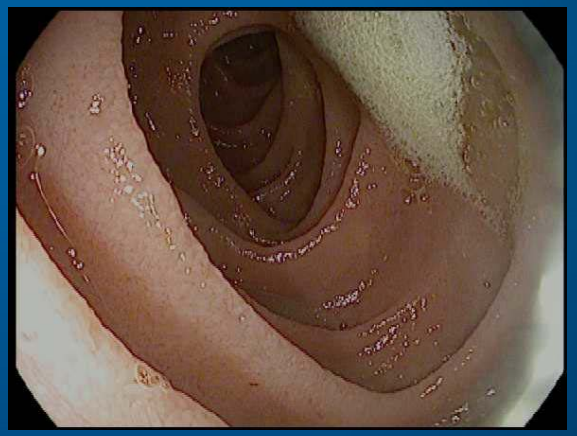
1.16.17 first restaging on pembrolizumab

71-Year-Old Woman, Former Smoker with Metastatic NSCLC and PD-L1 Positivity >50% (Ms Goodwin)

Evaluation for autoimmune colitis







Colon

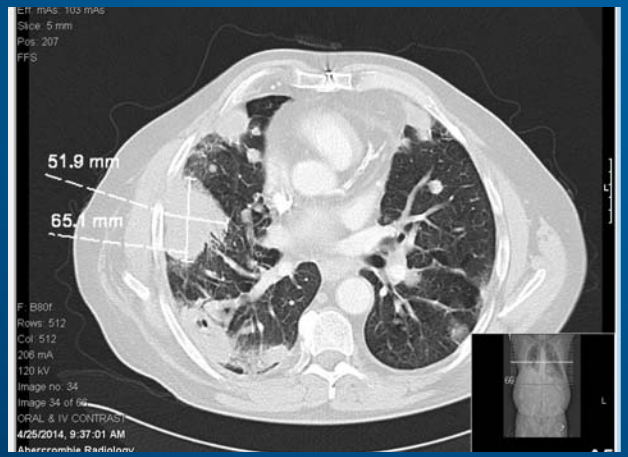
Duodenum

69-Year-Old Man, Heavy Smoker with Metastatic NSCLC and No Actionable Mutations (Ms Reed)

- 2/2011: Diagnosed with adenocarcinoma of the lung, right upper lobectomy
- Summer 2012: Surveillance CT — Multiple new lung nodules, biopsy-confirmed recurrence
- Carboplatin/pemetrexed with PD
- Carboplatin/docetaxel/bevacizumab followed by maintenance bevacizumab
- October 2013: CT revealed increase in size of pulmonary nodules in both lungs
- 12/2013 – 4/2014: Phase I trial of CHK-1 inhibitor
  - Developed inumerable bulky masses; heavy tumor burden
- 5/2014 – 7/2016: Phase III trial of nivolumab
  - CR after 1 year, discontinued therapy, remains NED

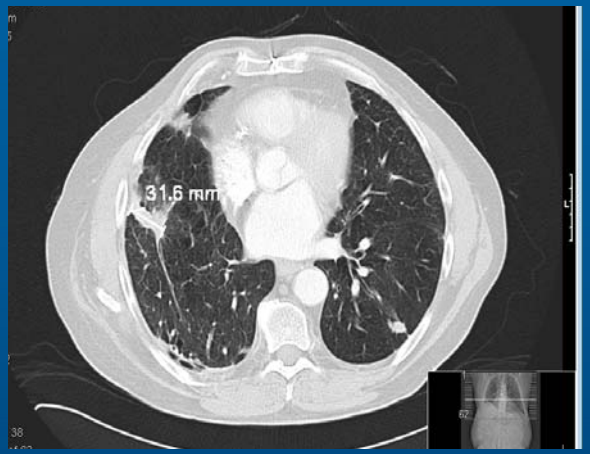
69-Year-Old Man, Heavy Smoker with Metastatic NSCLC and No Actionable Mutations (Ms Reed)

Pretreatment

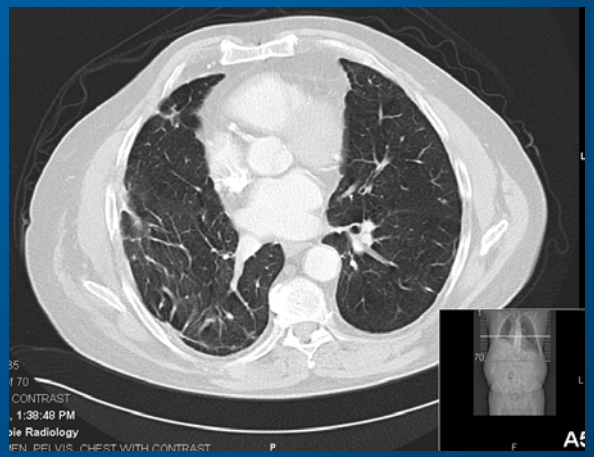


April 2014

Post-treatment



July 2014



December 2014

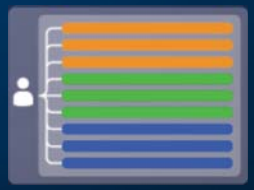

COPY PAPER

Module 8:
Pan-Wild-Type Squamous Metastatic NSCLC


Early-Stage NSCLC
Locally Advanced NSCLC
EGFR-Mutant Metastatic NSCLC
ALK-Mutant Metastatic NSCLC
Other Targetable Mutations in Metastatic NSCLC
Pan-Wild-Type Nonsquamous Metastatic NSCLC
Pan-Wild-Type Squamous Metastatic NSCLC

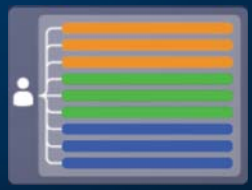
Key Considerations

- Choice of chemotherapy: selection of taxane — paclitaxel versus *nab* paclitaxel
- Necitumumab combined with chemotherapy
- Ramucirumab combined with chemotherapy



Choice of Chemotherapy: Selection of Taxane

- Paclitaxel
- *Nab* paclitaxel
  - No corticosteroid premedication with *nab*/P
  - Shorter infusion time with *nab*/P
  - Incidence, severity and reversibility of neuropathy?
  - Myelosupression?
  - Less Grade ≥3 neutropenia, arthralgias and neuropathy with *nab*/P
  - More Grade ≥3 thrombocytopenia and anemia with *nab*/P



Necitumumab

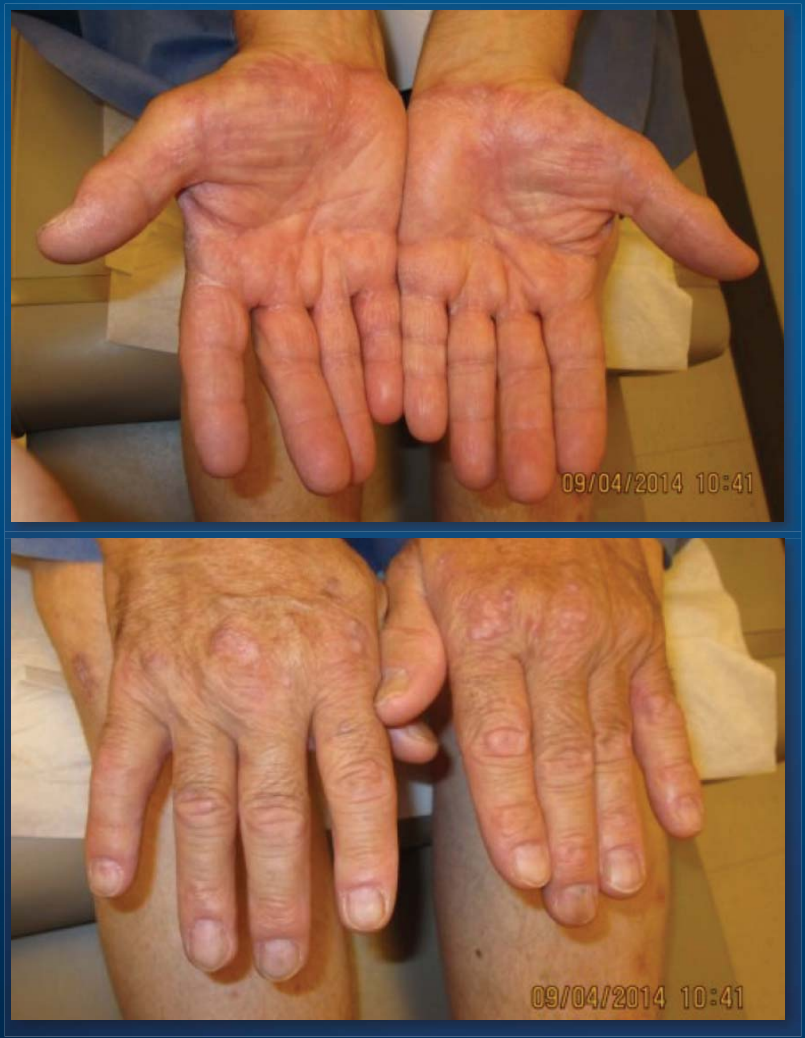
- Epidermal growth factor receptor (EGFR) monoclonal antibody
- Phase III SQUIRE study demonstrated an improvement in survival with the addition of necitumumab to first-line cisplatin/gemcitabine in patients with metastatic squamous cell NSCLC
  - Median OS: 11.5 vs 9.9 mos, HR = 0.84
- More Grade 3/4 hypomagnesemia and rash observed with necitumumab
- Approved as in the SQUIRE setting and population

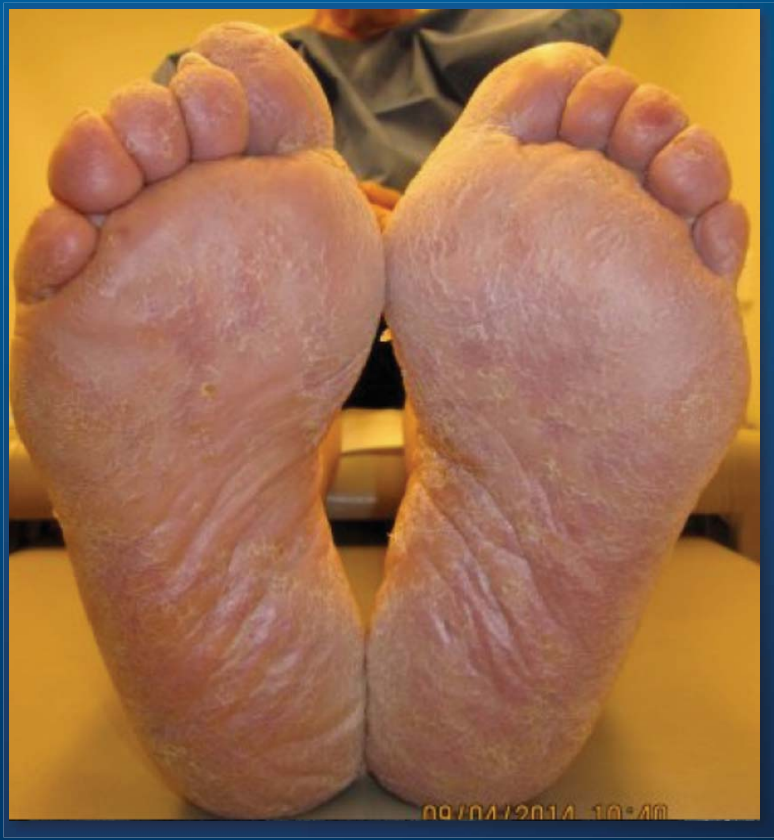
Thatcher N et al. *Lancet Oncol* 2015;16(7):763-74.

75-Year-Old Man, Former Smoker with Metastatic Squamous NSCLC (Ms Goodwin)

- 2012: Stage III+ squamous NSCLC with multiple positive nodes
  - Carboplatin/paclitaxel → RT, great response, surveillance q3m
- 5/2013: Local recurrence treated with SBRT
- 2/2014: Metastatic disease in both lungs with positive nodes
- CR on clinical trial of carboplatin/*nab* paclitaxel/atezolizumab → maintenance atezolizumab
  - Neuropathy, with impaired gait and falls; dermatitis
- 6/2016: Admitted with asymptomatic pancreatitis
- 8/2016: Re-admitted with asymptomatic hepatitis, worsening glucose control (h/o DM)
  - Liver biopsy-confirmed autioimmune hepatitis
- Currently NED, with no systemic therapy since 6/2016

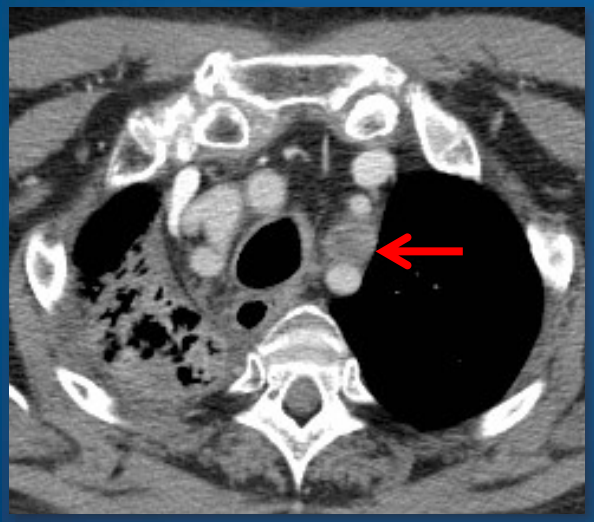
75-Year-Old Man, Former Smoker with Metastatic Squamous NSCLC (Ms Goodwin)



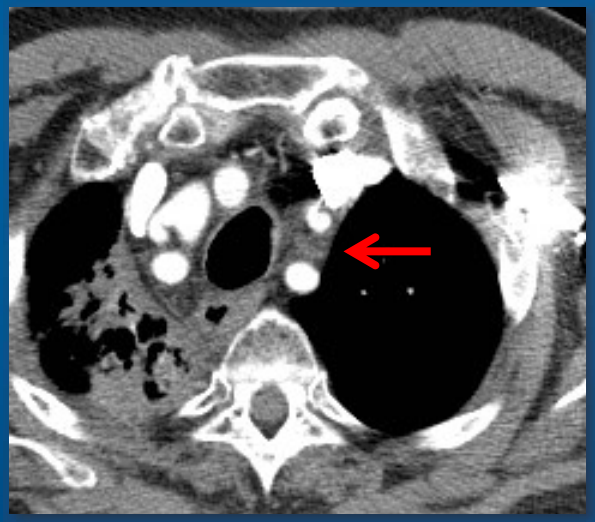


Lichenoid Interface Dermatitis

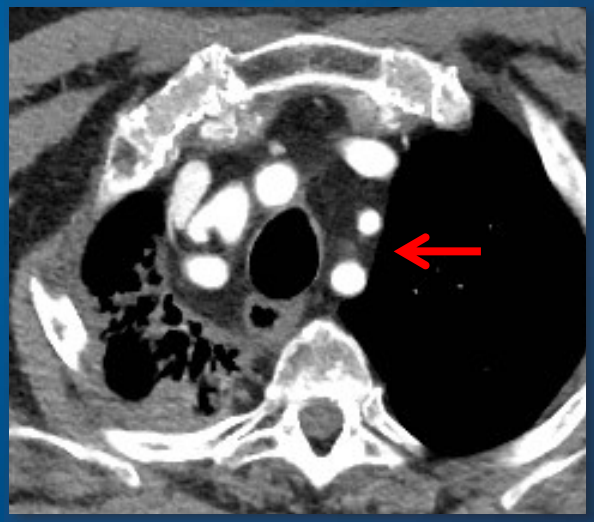
75-Year-Old Man, Former Smoker with Metastatic Squamous NSCLC (Ms Goodwin)



2.3.14 baseline



4.17.14
First restaging
On carboplatin/*nab*
paclitaxel/atezolizumab



4.7.17 most recent scan,
no evidence of disease

Reminder

Please turn in your CNE course evaluation for credit as you exit the activity.

Thank you for joining us.