# Monthly Oncology Tumor Boards: A Multidisciplinary Approach to Individualized Patient Care – Lung Cancer: Advanced Disease

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## Faculty Biography

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# CASE 1—NO MOLECULAR ALTERATION INITIALLY IDENTIFIED

## No molecular alteration identified

- In 2009, a 47-year-old Caucasian female presented to her primary care physician with cough and dyspnea that did not improve with an initial course of antibiotics
- She has a 10 pack year smoking history, less than ½ pack per day for 20 year and quit in 2002
- Chest x-ray showed a right hilar mass and left lung infiltrate
- CT scan of the chest demonstrated small bilateral pleural effusions with a 1.5 cm left lower lobe infiltrate and right paratracheal and bilateral hilar lymphadenopathy, and large pericardial effusion
- She underwent pericardial window and biopsy
- Pathology demonstrated metastatic adenocarcinoma—TTF-1 positive, CK7 positive, CK20 negative
- Molecular testing showed *EGFR* and *KRAS* wild type (2009)

## No molecular alteration identified

- PET/CT scan showed a left lower lobe nodule with increased FDG uptake and significant in the right paratracheal and bilateral hilar lymph nodes
- MRI of the brain did not show evidence of metastasis
- TNM stage was T1aN3M1a adenocarcinoma

- She initiated chemotherapy with carboplatin/paclitaxel and a study drug on clinical trial with partial response

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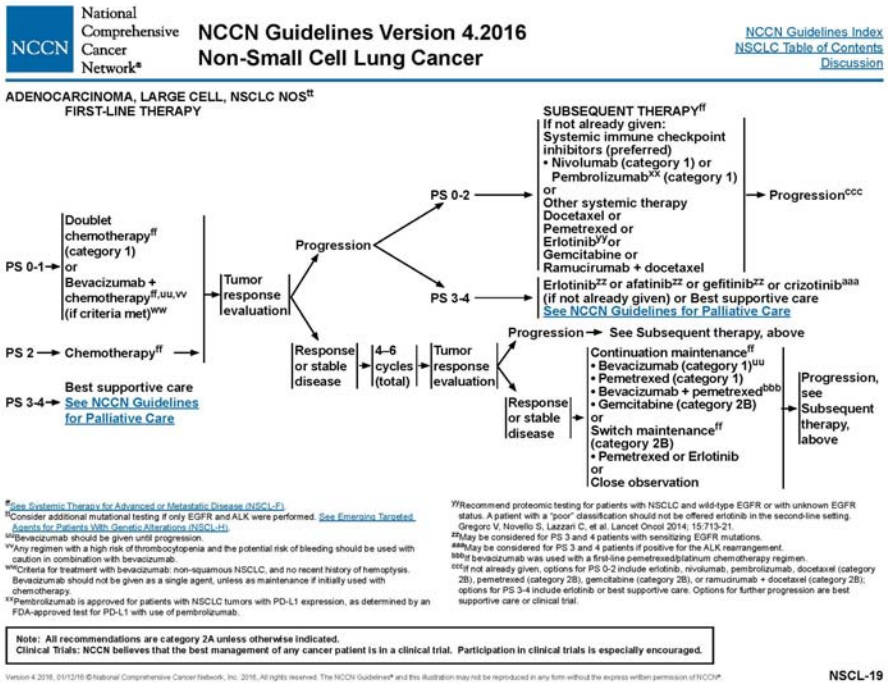
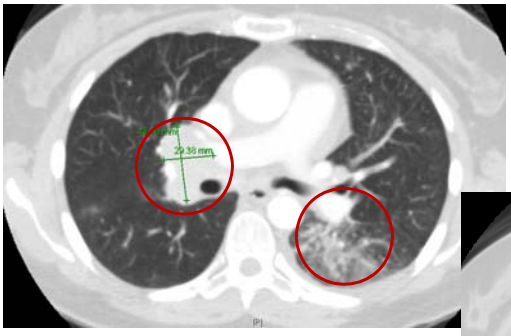
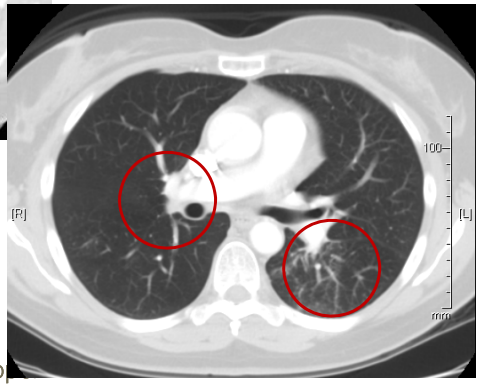


## No molecular alteration identified—Response to first line chemotherapy



Diagnosis, July 2009

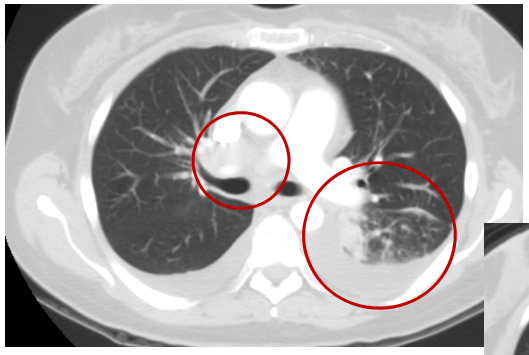
Response, October 2009



## No molecular alteration identified

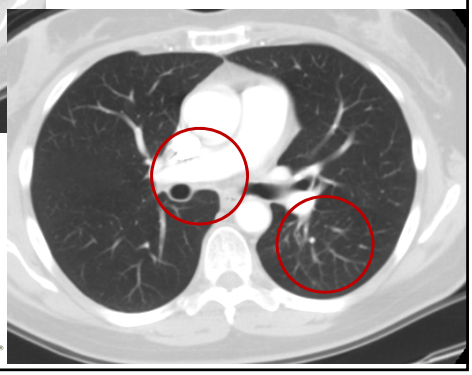
- Progression developed after 8 months,
- Brief treatment with erlotinib and immediate progression
- *ALK/ROS1* tested by FISH and negative
- Started treatment with pemetrexed  with PR
- Received 30 cycles (2010-2012) followed by progression within the lung, increasing fatigue and toxicities from cytotoxic therapy

## No molecular alteration identified—Response to second line chemotherapy



Progression, Feb 2010

Response, Dec 2010

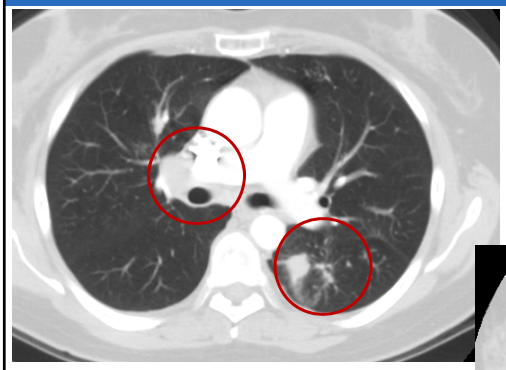


## No molecular alteration identified

- 2012, Further molecular testing sent and found to have V600E *BRAF* mutation
- Initiated vemurafenib with improvement,
- Discontinued due to dermatologic toxicity
- Initiated dabrafenib with response

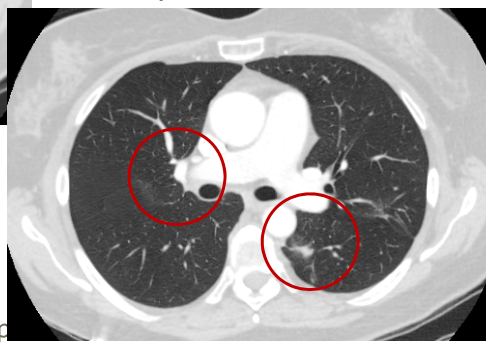
- The landscape of genetic alterations is constantly evolving and evaluation of new biomarkers is essential as patients live longer with advanced NSCLC

## No molecular alteration identified—Response to first line chemotherapy

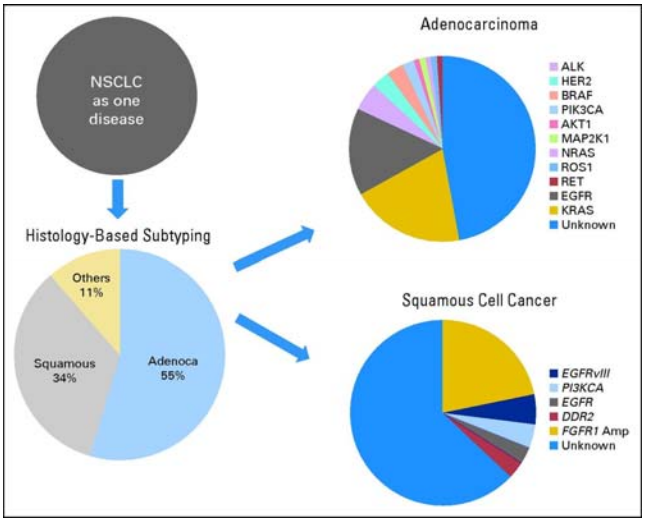


Progression, August 2012

Response, Jan 2013



## Evolution of NSCLC subtyping from histologic to molecular based




Li T et al. JCO 2013;31:1039-1049

# Dabrafenib/Trametinib for *BRAF* V600E NSCLC

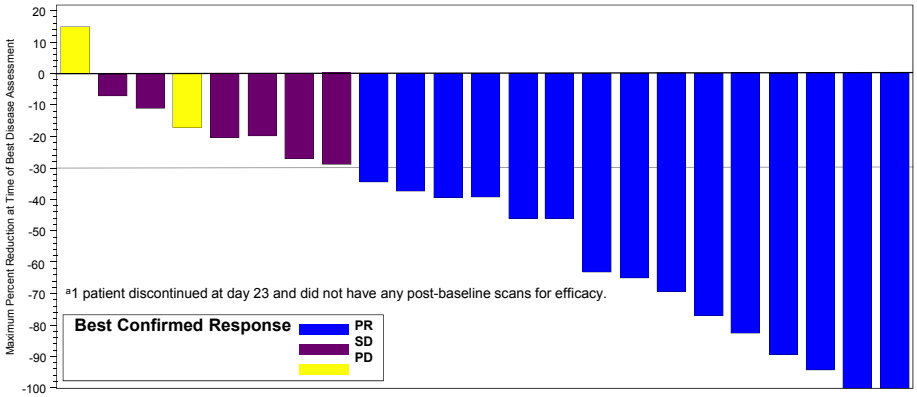
| | | All Treated (N = 33) |
|---|---|---|
| Age, years | Median (range) | 66 (49-88) |
| Sex, (%) | Female/male | 21 (64)/12 (36) |
| Race,[a] n (%) | White | 27 (82) |
| | Asian | 3 (9) |
| | African American/Mixed | 2 (6) |
| ECOG PS at baseline, n (%) | 0 or 1 | 31 (94) |
| | 2 | 2 (6) |
| Smoking history,[b] n (%) | Never smoked | 9 (27) |
| | ≤ 30 pack-years | 13 (39) |
| | > 30 pack-years | 10 (30) |
| Number of prior systemic regimens for metastatic disease,[c] n (%) | 1 | 19 (58) |
| | 2 | 6 (18) |
| | 3 | 5 (15) |

[a]One patient had missing race data; [b]One patient had missing smoking history information; [c]Three patients had missing information for prior systemic regimen for metastatic disease.



# Dabrafenib/Trametinib for *BRAF* V600E NSCLC

## Maximum Reduction of Sum of Lesion Diameters By Best Confirmed Response in ≥ 2nd Line (N = 24[a])



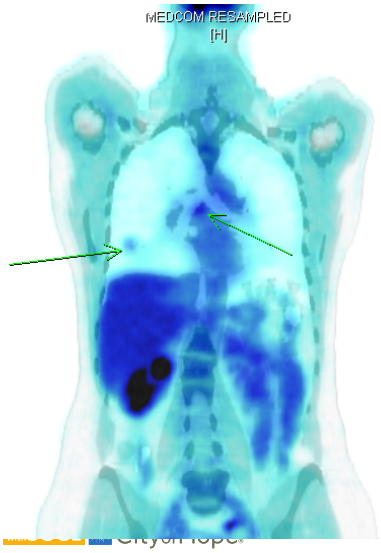

- The median duration of response was not reached

# CASE 2—RECURRENCE AFTER CONCURRENT CHEMORADIATION

## De novo EGFR TKI resistance, alternative options

- 50-year-old woman presented with progressive right neck swelling in 2007
- Her primary care physician referred her for biopsy
- CT of the neck and chest demonstrated a 2.6 cm right supraclavicular lymph node, mediastinal lymphadenopathy and a 1.2 cm right lower lobe nodule
- Biopsy of the supraclavicular LN and lung nodule both demonstrated adenocarcinoma, TTF1+ and CK7 +, CK20-
- Brain MRI was negative for metastatic disease
- TNM stage was T1aN3M0

# Stage IIIB NSCLC diagnosis 10/07



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## NCCN Guidelines Version 4.2016
## Non-Small Cell Lung Cancer

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| CLINICAL ASSESSMENT | PRETREATMENT EVALUATION | INITIAL TREATMENT |
|---|---|---|
| Stage IIIB (T1–3, N3) | • PFTs (if not previously done)<br>• FDG PET/CT scan[j] (if not previously done)<br>• Brain MRI with contrast<br>• Pathologic confirmation of N3 disease by:<br>▸ Mediastinoscopy<br>▸ Supraclavicular lymph node biopsy<br>▸ Thoracoscopy<br>▸ Needle biopsy<br>▸ Mediastinotomy<br>▸ EUS biopsy<br>▸ EBUS biopsy | N3 negative → See Initial treatment for stage I–IIIA (NSCL-8)<br>N3 positive → Definitive concurrent chemoradiation[l,q,u] (category 1)<br>Metastatic disease → See Treatment for Metastasis limited sites (NSCL-13) or distant disease (NSCL-15) |

[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
[l]See Principles of Radiation Therapy (NSCL-C)
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E)
[u]If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

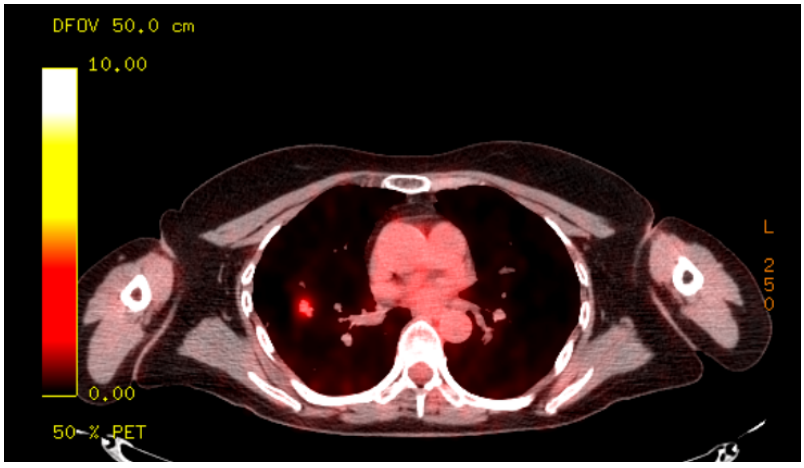
**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**

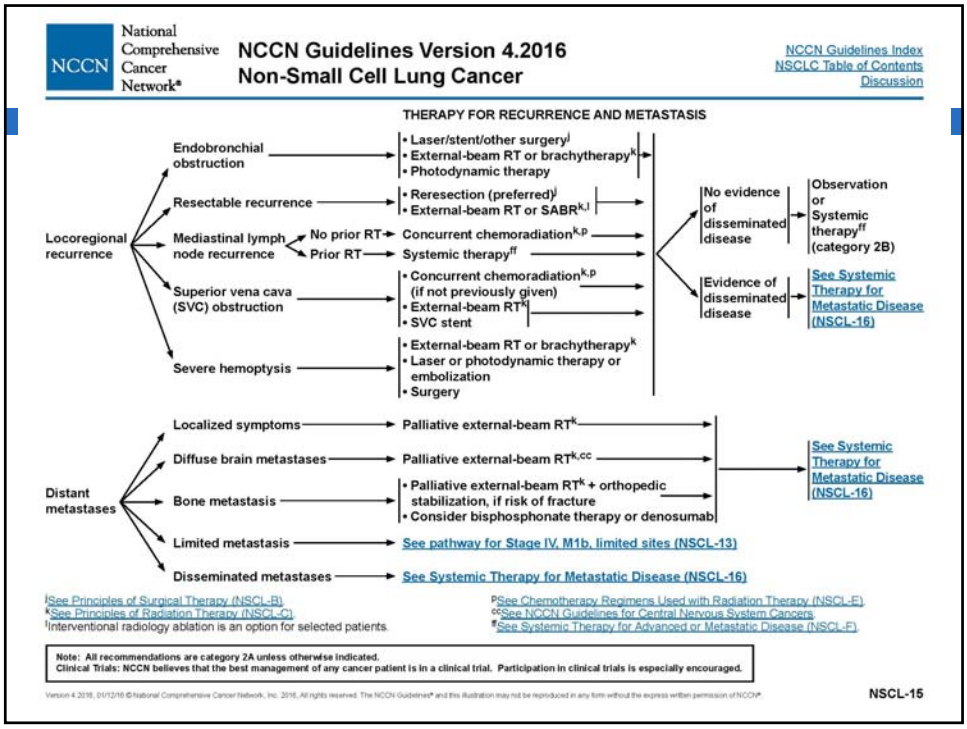
## De novo resistance, alternative options

- She received concurrent chemoradiotherapy with cisplatin and etoposide, completed in early 2008
- She was followed with surveillance CT scans and remained without evidence of disease until 2012
- March 2012, CT demonstrated growth in the left lower lobe nodule
- PET/CT showed uptake in the left lower lobe without evidence of lymph node or distant spread
- MRI of the brain was negative
- Biopsy demonstrated adenocarcinoma



## Localized pulmonary recurrence (3/12)

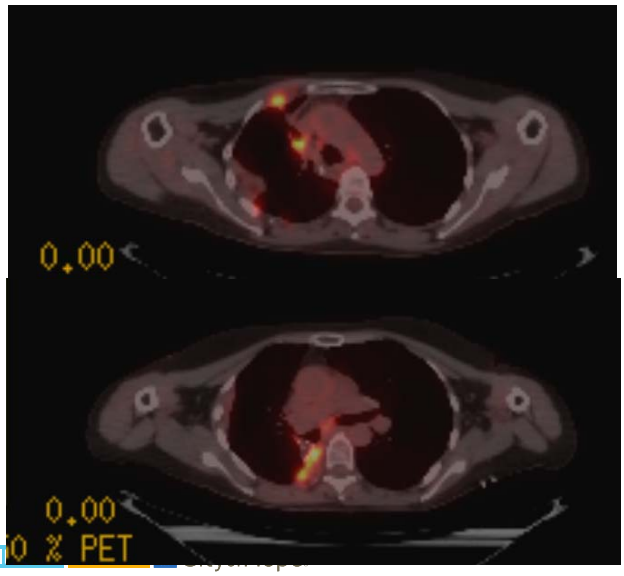





## De novo EGFR TKI resistance

- She underwent right lower lobectomy in 4/2012, and lymph nodes were negative for recurrence
- Molecular testing demonstrated an insertion mutation in exon 20 of the *EGFR* gene (Ala767_Val769dup) consistent with resistance to EGFR TKI therapy
- She was monitored of therapy
- In March 2014, she developed metastatic recurrence in the lung and abdominal lymph nodes
- Brain MRI was negative
- Biopsy demonstrated recurrent adenocarcinoma with the same exon 20 insertion in *EGFR*

## Metastatic progression in the lung and abdominal lymph nodes (3/14)




## De novo resistance, alternative options

- She was assessed for clinical trial with an anti-PD-L1 antibody
- PD-L1 expression was positive
- She initiated an anti-PD-L1 antibody in 5/2014
- The tumor progressed in the right axillary lymph node 11/2014 and she continued on therapy post-progression
- LN biopsy demonstrated adenocarcinoma
- She remained on anti-PD-L1 therapy for 18 months

# CASE 3—ALK TKI RESISTANCE

## *ALK* acquired resistance

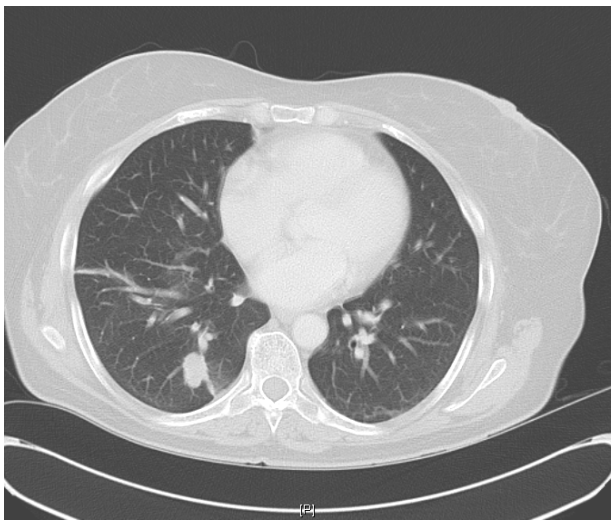
- 52-year-old female presented with neck discomfort
- Chest x-ray demonstrated a deviation of the trachea
- CT scan of the chest showed a 1.9 cm right lower lobe mass
- In addition, extensive thrombosis in the right internal jugular vein, prominent right supraclavicular lymph nodes, right mediastinum and hilar lymph nodes, subcarinal lymph node 2.9 cm
- PET scan demonstrated increased FDG uptake in the right lower lobe mass, and subcarinal, precarinal, right paratracheal and right supraclavicular LNs
- MRI of the brain showed no evidence of metastatic disease

## *ALK* acquired resistance

- Right lung biopsy demonstrated moderately differentiated adenocarcinoma,
- TTF-1 diffuse nuclear positivity, CK20 negative, CK7 positive,
- Right supraclavicular lymph node demonstrated metastatic poorly differentiated carcinoma
- Molecular testing: *EGFR* and *KRAS* wild type; *ALK* with translocation by FISH
- TNM stage was IIIB, T1aN3M0

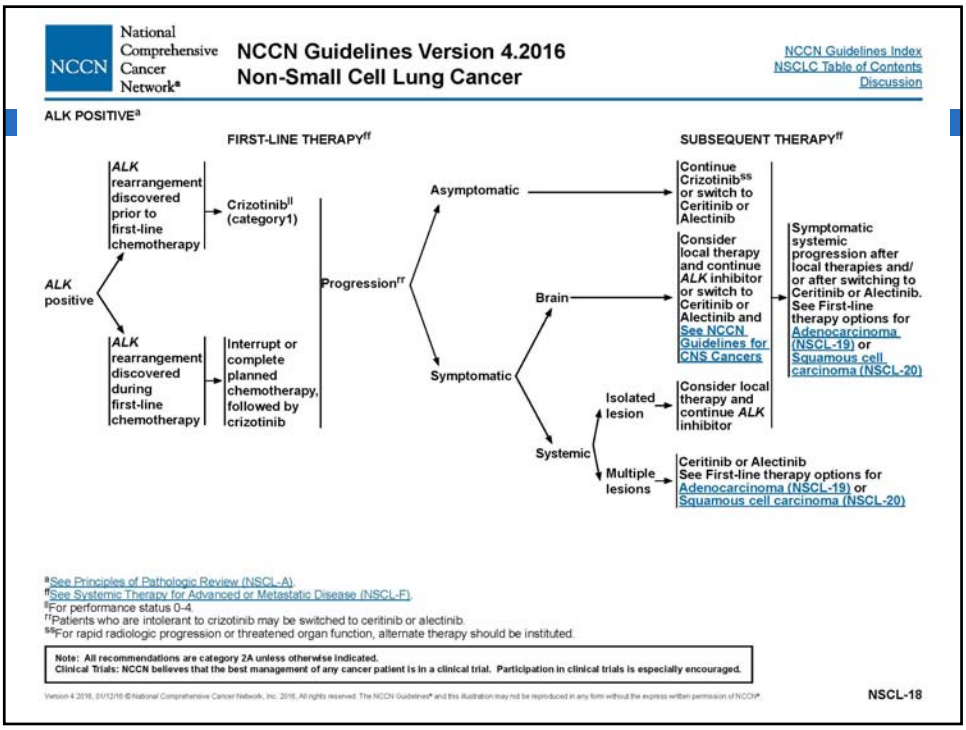


## Primary diagnosis, stage IIIB (10/12)



# *ALK* acquired resistance

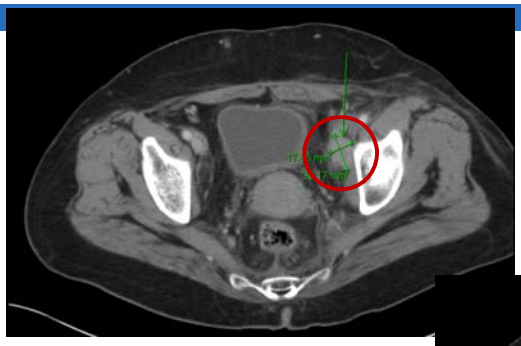
- Treatment with concurrent chemotherapy and radiation was given with  weekly carboplatin and paclitaxel, followed by 2 cycles of carboplatin and paclitaxel consolidation completed in early 2013.
- The tumor progressed within the lung and crizotinib initiated in 4/2013
- She developed progression with life-threatening DIC in May 2014
- She initiated pemetrexed in 5/2014 and received 8 cycles through 10/2014 with progression in pelvic lymph nodes and increasing lower extremity edema



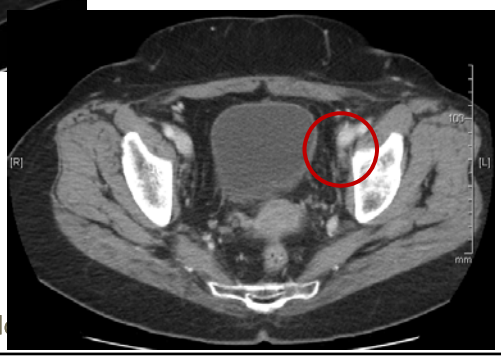
## *ALK* acquired resistance

- Treatment started on a phase II trial with brigatinib in 11/2014
- Achieved complete response…

## Progression post crizotinib and pemetrexed



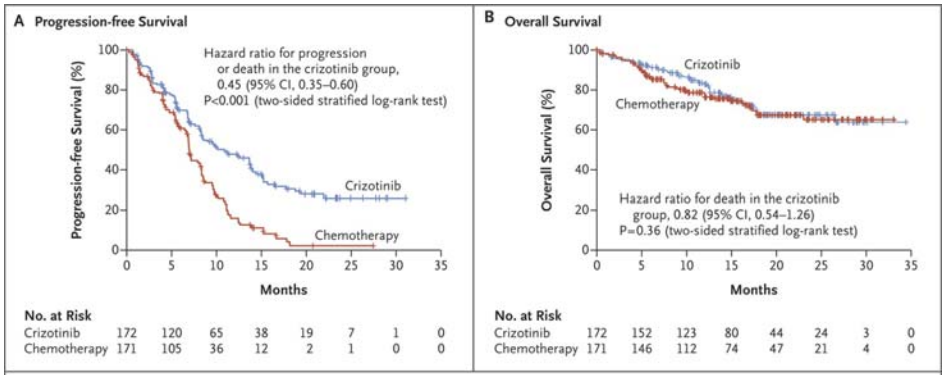
Pre-treatment



Brigatinib, 8 weeks

CR

# Crizotinib as first-line therapy




Solomon BJ et al. N Engl J Med 2014;371:2167-2177

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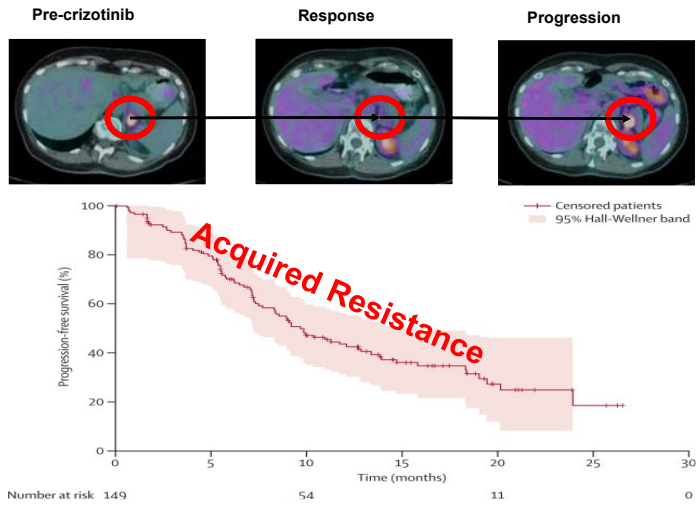
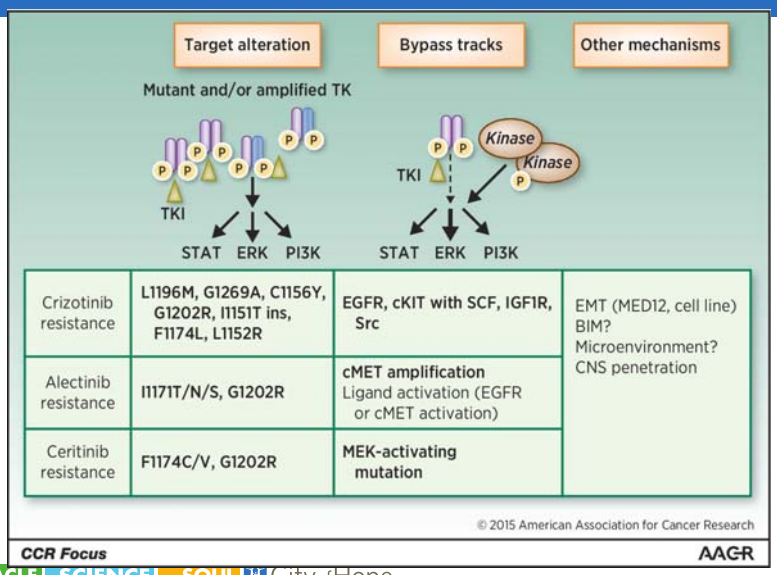
# Invariably, acquired resistance emerges




theMIRACLE ofSCIENCE withSOUL CityofHope Camidge et al., Lancet Onc 2012

# Mechanisms of acquired resistance to ALK inhibitor therapy




| | | | |
|---|---|---|---|
| Crizotinib resistance | L1196M, G1269A, C1156Y, G1202R, I1151T ins, F1174L, L1152R | EGFR, cKIT with SCF, IGF1R, Src | EMT (MED12, cell line)<br>BIM?<br>Microenvironment?<br>CNS penetration |
| Alectinib resistance | I1171T/N/S, G1202R | cMET amplification<br>Ligand activation (EGFR or cMET activation) | |
| Ceritinib resistance | F1174C/V, G1202R | MEK-activating mutation | |



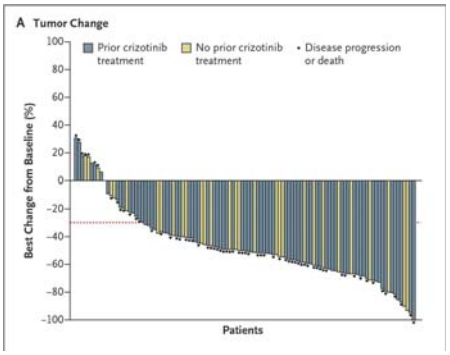
CCR Focus AACR

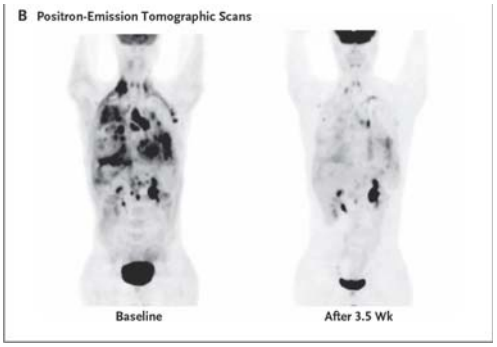
Ryohei Katayama et al. Clin Cancer Res 2015;21:2227-2235

# Next-generation ALK TKIs

| ALK TKI | Status | Ongoing Studies |
|---|---|---|
| Ceritinib | FDA Approved | Phase 3 v. chemo |
| Alectinib | FDA Approved | Phase 3 v. crizotinib |
| Brigatinib | Investigational<br>FDA Breakthrough | Phase 2 |
| X-396 | Investigational | Phase 1/2a |
| TSR-011 | Investigational | Phase 1/2a |
| RXDX-101 | Investigational | Phase 1/2a |
| PF-06463922 | Investigational | Phase ½ |
| CEP-37440 | Investigational | Phase 1 |

## Response to Ceritinib, most post crizotinib

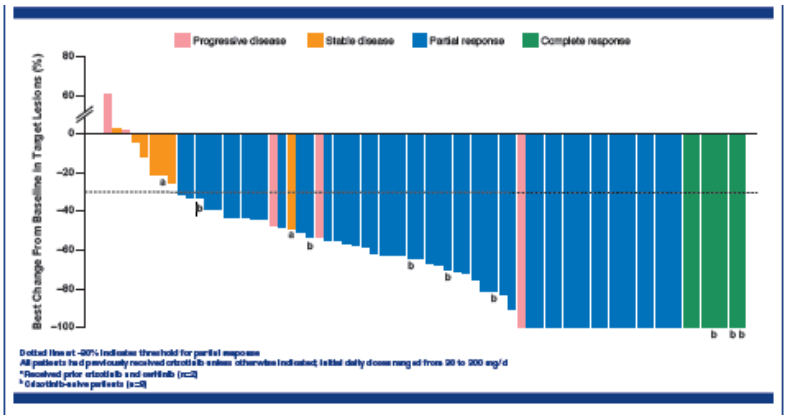



Shaw AT et al. N Engl J Med 2014;370:1189-1197

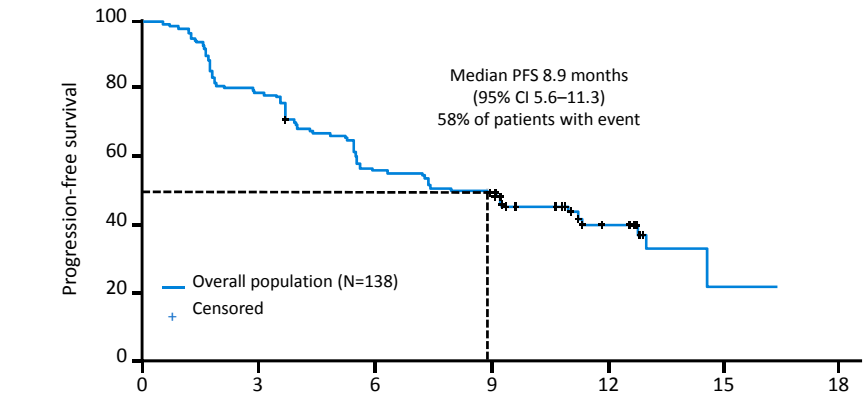


## Brigatinib responses following crizotinib in *ALK* + NSCLC




Camidge et al J Clin Oncol 2015 (abstract 8062)

# Progression-free survival with alectinib in crizotinib-resistant *ALK*+ NSCLC patients




| No. at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Overall population | 138 | 109 | 76 | 65 | 17 | 1 | – |

Updated analysis cut-off 8 Jan 2015

Gadgeel SM Lancet Oncol 2014; Ou SH J Clin Oncol 2016

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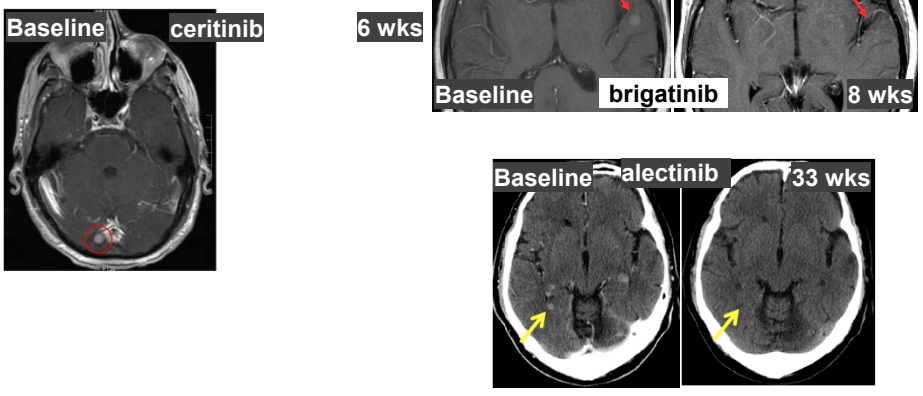
# Ceritinib, brigatinib, and alectinib show antitumor activity in *ALK*+ NSCLC with brain metastasis

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Mehra et al., ASCO (2012), abstr 3007
Gettinger et al., ESMO (2012), abstr 4390
Nishio et al., ESMO (2012), abstr 4410

# CASE 4—SECOND LINE THERAPY FOR SQUAMOUS CELL NSCLC

## Second line therapy for squamous cell NSCLC

- 57-year-old man with progressive chest discomfort and dyspnea for 4 months
- 40 pack-year smoking history, quit 3 months ago
- CT chest/abdomen demonstrates right lung mass with multiple soft tissue nodules on the abdomen and scalp
- PET/CT shows uptake in the right lung, mediastinal lymph nodes and multiple subcutaneous nodules
- MRI of the brain had no metastases

## Second line therapy for squamous cell NSCLC

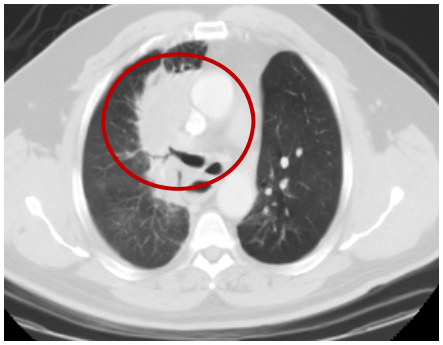
- Biopsy specimen of a soft tissue nodule confirms squamous cell carcinoma (TTF-1 neg, p63 +)
- ECOG PS 0
- He initially received cisplatin and gemcitabine for 4 cycles with initial response followed by progression



## Second line therapy for squamous cell NSCLC

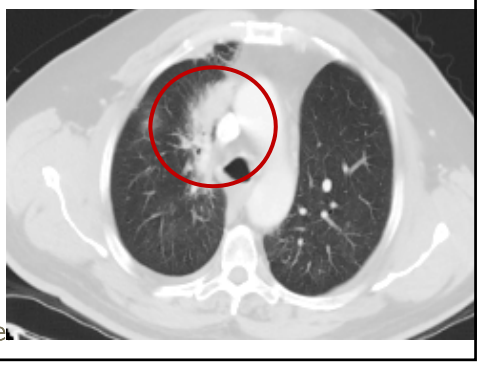
- He enrolled in a clinical trial and received nivolumab (anti–PD-1 antibody)
- He received 4 cycles with stable disease followed by development of pulmonary infiltrates and increased cough and dyspnea after cycle 8
- Interstitial pneumonitis was suspected
- Therapy was discontinued and prednisone 1mg/kg/day was started

# Second line therapy for squamous cell NSCLC



January 2013

May 2013



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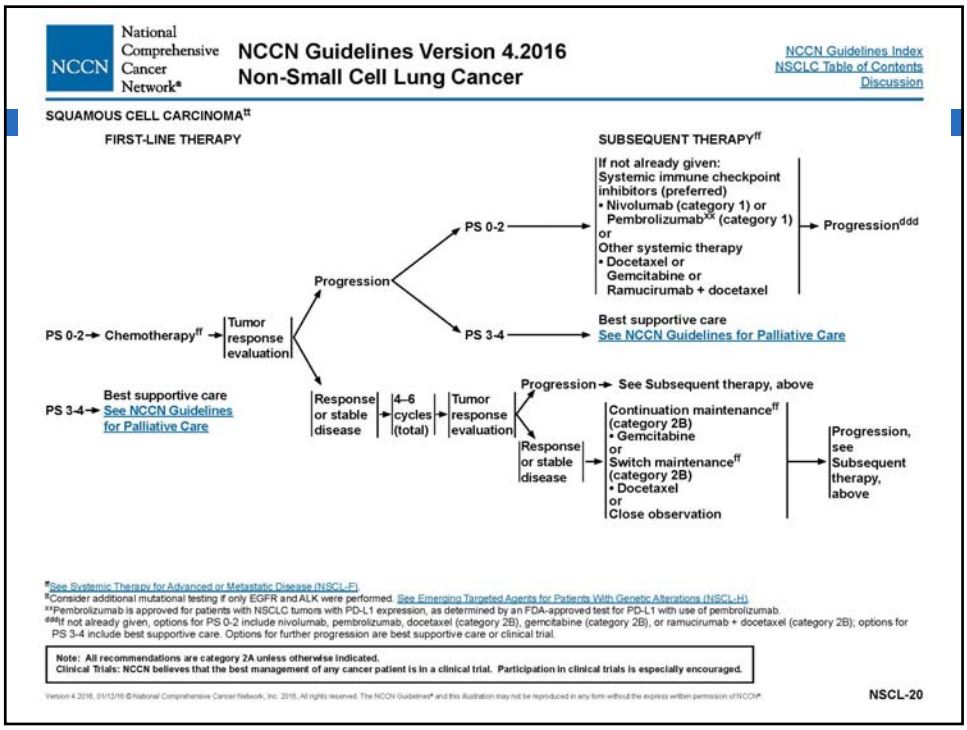

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**NCCN Guidelines Version 4.2016**
**Non-Small Cell Lung Cancer**

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**SQUAMOUS CELL CARCINOMA**[tt]

**FIRST-LINE THERAPY**

PS 0-2 → Chemotherapy[ff] → Tumor response evaluation
- Progression
  - PS 0-2 → Subsequent therapy
  - PS 3-4 → Best supportive care; See NCCN Guidelines for Palliative Care
- Response or stable disease → 4–6 cycles (total) → Tumor response evaluation
  - Progression → See Subsequent therapy, above
  - Response or stable disease → Continuation maintenance[ff] (category 2B): • Gemcitabine or Switch maintenance[ff] (category 2B): • Docetaxel or Close observation → Progression, see Subsequent therapy, above

PS 3-4 → Best supportive care; See NCCN Guidelines for Palliative Care

**SUBSEQUENT THERAPY**[ff]

If not already given:
Systemic immune checkpoint inhibitors (preferred)
• Nivolumab (category 1) or Pembrolizumab[xx] (category 1)
or
Other systemic therapy
• Docetaxel or Gemcitabine or Ramucirumab + docetaxel
→ Progression[ddd]

[tt] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ff] Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[xx] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.
[ddd] If not already given, options for PS 0-2 include nivolumab, pembrolizumab, docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

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



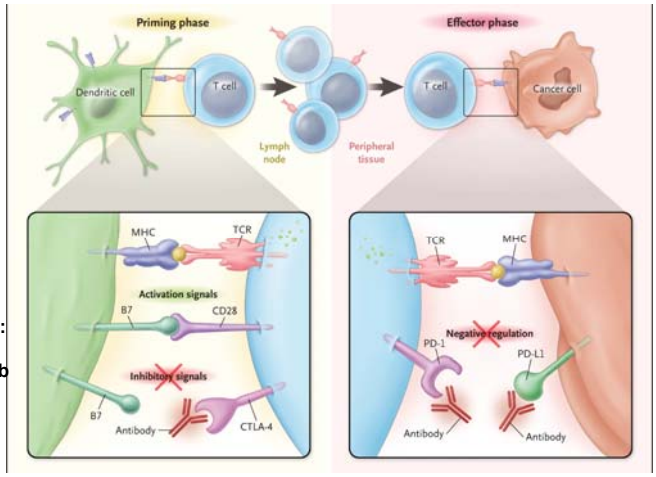
NSCL-20

## Second line therapy for squamous cell NSCLC

- He was monitored with supportive care and returned 1 month later with improving symptoms and steroids were tapered
- Repeat imaging demonstrated decrease in the primary lung tumor
- He remained asymptomatic off therapy for 6 months following discontinuation of nivolumab

## CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

**CTLA-4 mAbs:**
**Ipilimumab**
**Tremelimumab**



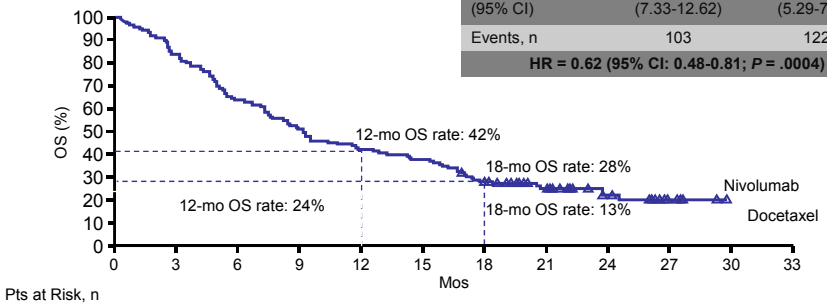

**PD-1 mAbs:**
**Nivolumab**
**Pembrolizumab**

**PD-L1 mAbs:**
**Atezolizumab**
**Avelumab**
**Durvalumab**

Ribas A. N Engl J Med. 2012;366:2517-2519.

## Nivolumab vs Docetaxel in Advanced SQ NSCLC (CheckMate 017): OS

| | Nivolumab (n = 135) | Docetaxel (n = 137) |
|---|---|---|
| Median OS, mos (95% CI) | 9.2 (7.33-12.62) | 6.0 (5.29-7.39) |
| Events, n | 103 | 122 |
| HR = 0.62 (95% CI: 0.48-0.81; *P* = .0004) | | |




Pts at Risk, n

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 135 | 113 | 86 | 69 | 57 | 51 | 37 | 25 | 14 | 6 | 0 | 0 |
| Docetaxel | 137 | 104 | 69 | 46 | 33 | 22 | 17 | 11 | 7 | 3 | 1 | 0 |

- Minimum follow-up for survival: 18 mos

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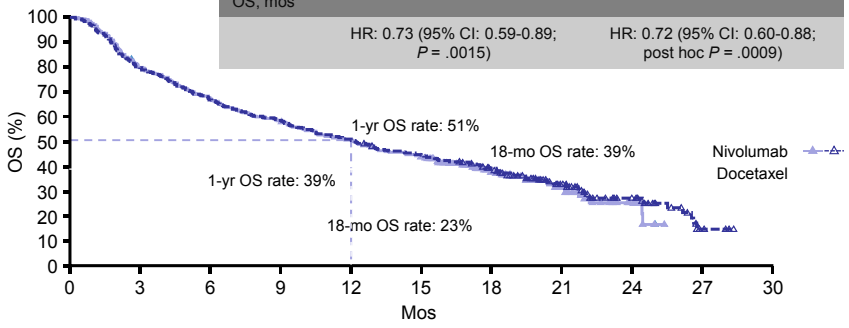
Reckamp K, et al. WCLC 2015. ORAL02.01.
Brahmer J, et al. NEJM 2015

## Nivolumab vs Docetaxel in Advanced Non-SQ NSCLC (CheckMate 057): OS

| | 12-Mo OS | | 18-Mo OS | |
|---|---|---|---|---|
| | Nivo (n = 292) | Doc (n = 290) | Nivo (n = 292) | Doc (n = 290) |
| Median OS, mos | 12.2 | 9.4 | 12.2 | 9.4 |
| | HR: 0.73 (95% CI: 0.59-0.89; *P* = .0015) | | HR: 0.72 (95% CI: 0.60-0.88; post hoc *P* = .0009) | |




- Minimum follow-up for 12-mo OS rate: 13.2 mos; for 18-mo OS rate: 17.1 mos

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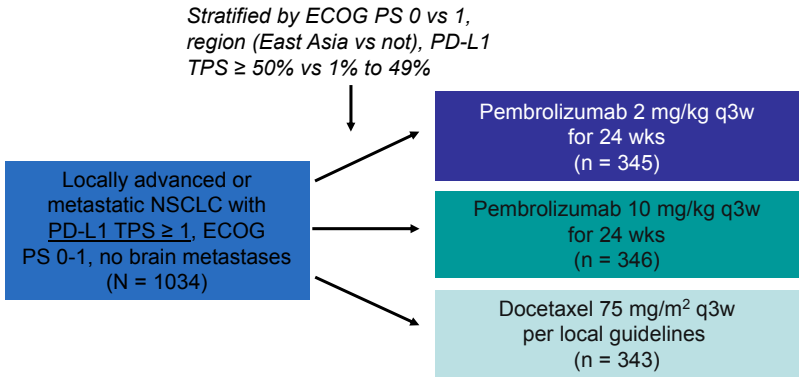
Horn L, et al. ESMO 2015. Abstract 3010.
Borghaei H, et al. 2015

## Pembrolizumab vs Docetaxel in Previously Treated PD-L1+ Advanced NSCLC (KEYNOTE-010)




- Primary endpoints*: PFS, OS
- Secondary endpoints*: ORR, DoR, safety

*In both the PD-L1 TPS ≥ 1% and ≥ 50% populations.

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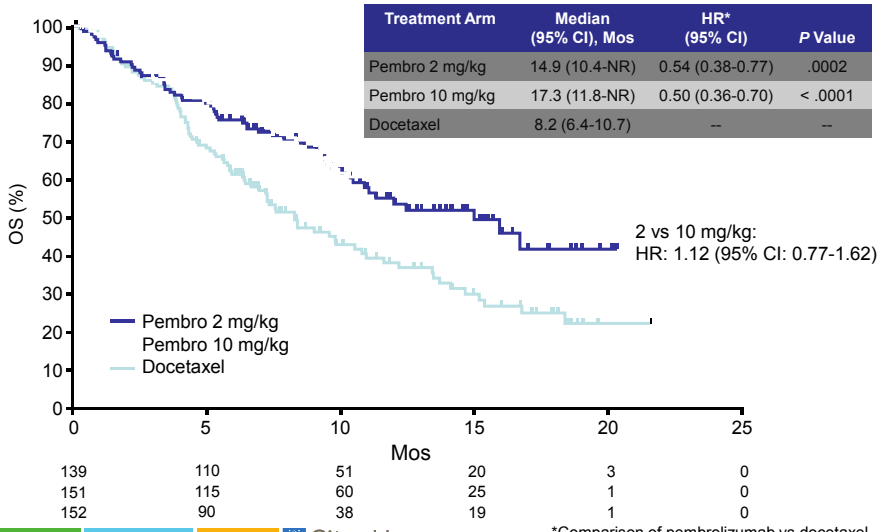
Herbst R, et al. Lancet. 2015;[Epub ahead of print].

## KEYNOTE-010: OS for PD-L1 TPS ≥ 50% Stratum

| Treatment Arm | Median (95% CI), Mos | HR* (95% CI) | *P* Value |
|---|---|---|---|
| Pembro 2 mg/kg | 14.9 (10.4-NR) | 0.54 (0.38-0.77) | .0002 |
| Pembro 10 mg/kg | 17.3 (11.8-NR) | 0.50 (0.36-0.70) | < .0001 |
| Docetaxel | 8.2 (6.4-10.7) | -- | -- |

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*Comparison of pembrolizumab vs docetaxel.

Herbst R, et al. Lancet. 2015;[Epub ahead of print].