

# Clinical Updates and Issues: Advanced Non-Small Cell Lung Cancer

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The Ohio State University Comprehensive Cancer Center  
– James Cancer Hospital and Solove Research Institute



[NCCN.org](http://NCCN.org) – For Clinicians | [NCCN.org/patients](http://NCCN.org/patients) – For Patients

## Learning Objectives

- Explain the complexities in treating advanced non-small cell lung cancer
- Analyze the potential of immunotherapies for treating advanced non-small cell lung cancer.
- Recognize and manage adverse events associated with therapies used to treat advanced non-small cell lung cancer.



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## Lung Cancer Statistics, 2016

- **Greatest cause of cancer deaths worldwide**
  - 230,390 new cases per year, 15% of US cancer cases
  - 158,890 deaths per year, 27% of US cancer deaths
- **More deaths than colon, breast, and prostate cancer deaths combined**

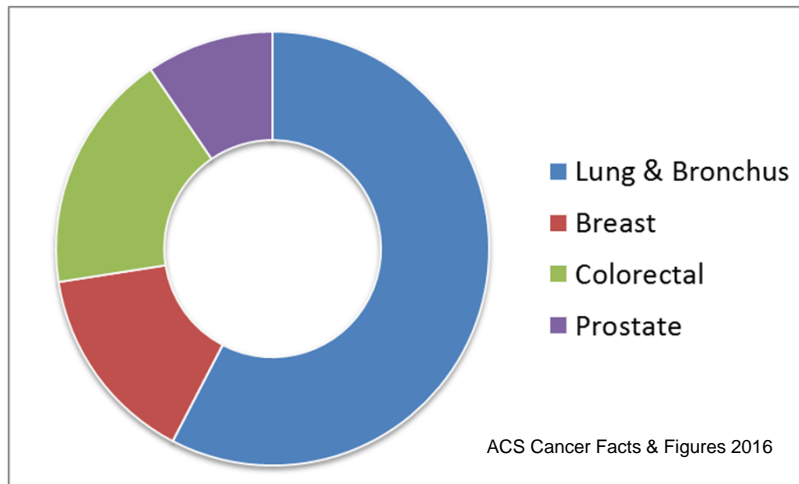
(ACS Cancer Facts & Figures, 2016)



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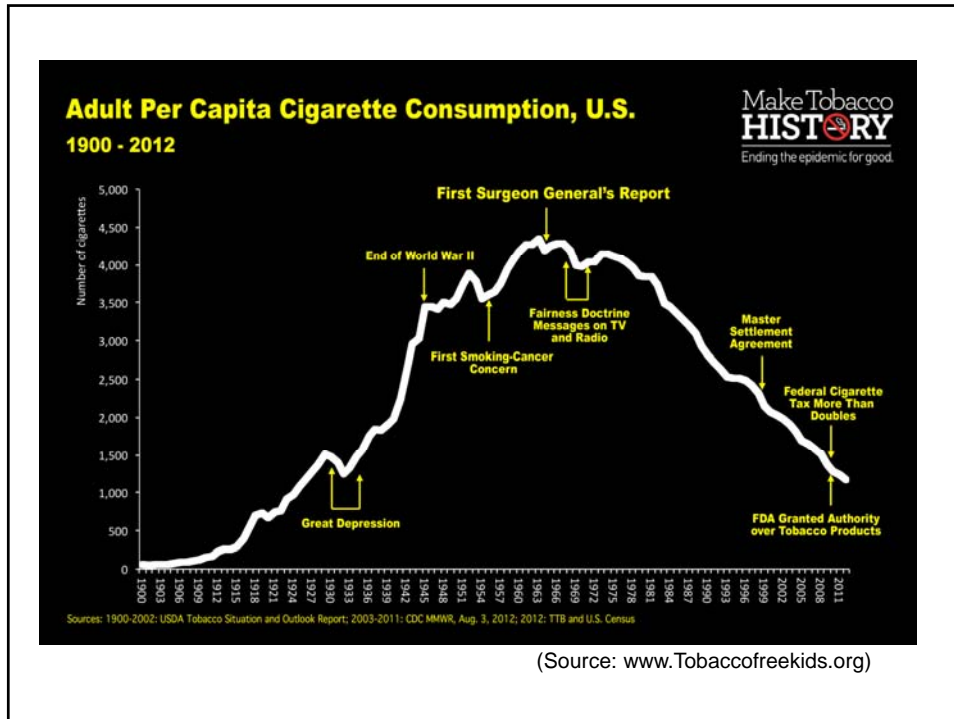
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## Estimated Cancer Deaths by Site



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## Clinical Symptoms and Presentation of Lung Cancer

- Cough
- Dyspnea / wheezing /SVC syndrome
- Hemoptysis
- Pneumonia / unresolved infection
- Pleural effusion
- Hoarseness
- Weight loss
- Night sweats
- Pain

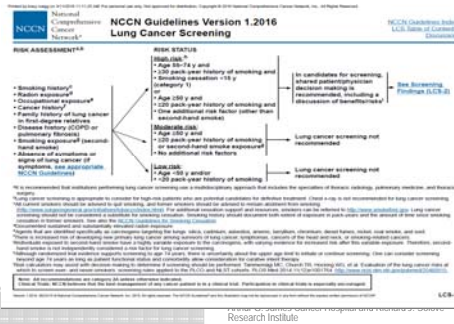
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# Lung Cancer Screening: NLST

- **National Lung Screening Trial (2002-2007/2009)**
- Clinical symptoms of lung cancer are a late finding
- Advanced tumor stage @ time of diagnosis= palliative treatment
- Low dose CT scan vs. CXR
- Annual screening x 3
- 27% CT vs. 6.2 % CXR (year 1) AND 16.8% CT vs. 5.0% CXR (year 2)
- Decreased advanced stage with increased early stage Dx.

Abele et al, 2011



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# Diagnostic Techniques

- **Adequate biopsy sample**
  - Fine Needle Aspiration (FNA) – CORE Bx
  - Bronchoscopy / EBUS
  - Video Assisted Thoracoscopic Surgery (VATS)
  - Mediastinoscopy
- **THE ISSUE IS TISSUE!**

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# Lung Cancer Pathology

- Small Cell- 15%
- Non-Small Cell- 85%
  - Adenocarcinoma
    - most common
    - least associated with tobacco
    - Molecular Mutations
  - Squamous cell carcinoma
  - Bronchoalveolar carcinoma / papillary?
  - Large-cell carcinoma
- Mixed tumors
- Carcinoid and rare tumors

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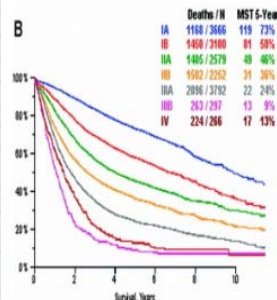


# Staging of Non Small Cell Lung Cancer

## 7<sup>th</sup> IASLC Staging System

T and M		N0	N1	N2	N3
UICC6 and descriptor	New T/M	Stg	Stg	Stg	Stg
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	IIA	IIIA	IIIB
T2 (>5-7 cm)	T2b	IIA	IIIB	IIIA	IIIB
T2 (>7 cm)		IIIB	IIIA	IIIA	IIIB
T3 invasion	T3	IIIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		IIIB	IIIA	IIIA	IIIB
T4 (extension)	T4	IIIA	IIIA	IIIB	IIIB
M1 (ipsilateral lung)		IIIA	IIIA	IIIB	IIIB
T4 (pleural effusion)	M1a	IV	IV	IV	IV
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Goldstraw et al, 2007



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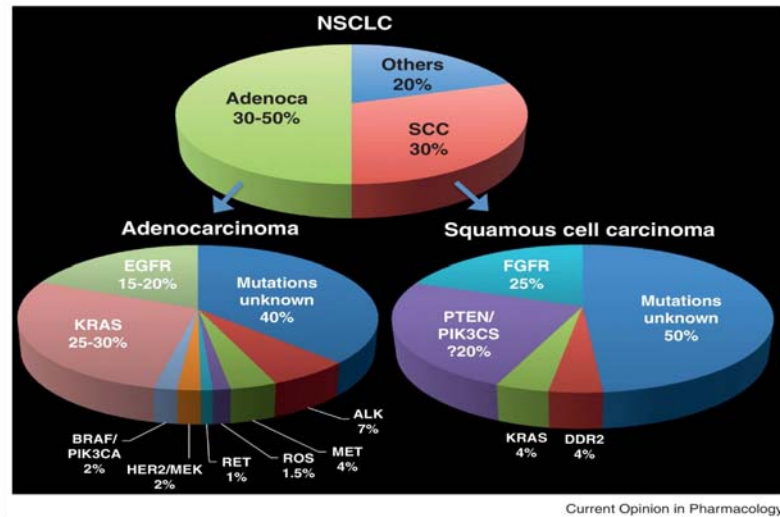


# Pulmonary Molecular Testing: Next Generation Sanger Sequencing

- FISH analysis: ALK / ROS1 / MET / RET
- EGFR (exons 19-21)
- T790m (exon 20) AKT1
- BRAF
- ERBB2, ERBB4
- HRAS, KRAS, NRAS
- HER2
- MEK
- PIK3CA, PTEN
- STK11
- TP53
- FDGF1, FGFR2
- CTNNB1
- DDR2
- MAP2K1
- NOTCH1
- SMAD4

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Alamgeer et al, 2013

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## Mutational Pathway Patient Characteristics

Molecular targets	Prevalence (%)	More commonly associated patient characteristics
RAS	30	Former/current smokers
EGFR	10–18 Caucasian; 40–55 Asian	East Asian, female, never smokers
ALK	3–7	Young, never smokers
ROS	1–2	Young, never smokers
RET	1–2	Never smokers
PIK3CA	2	Concurrent with other oncogenic drivers
BRAF	3–5	Former/current smokers
HER2	1–4	Female, never smokers
RIT	2 <sup>b</sup>	Not available
NTRK1	3 <sup>b</sup>	Female, never smokers
MET	11	Mutually exclusive with EGFR mutations
FGFR1	1–3	Male, smokers <sup>a</sup>

<sup>a</sup> not statistically significant

<sup>b</sup> Frequencies detected from pts. with unknown mutations; prevalence is an overestimation

Gower, Wang & Giaccone, 2014

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## Metastatic Disease

- **Stage IV**
- **Metastatic sites:**
  - bone
  - brain
  - liver
  - adrenal glands

### 5 year survival

<1%



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## Treatment Considerations

- **Diagnosis**
  - Adequate biopsy sample
- **Stage**
  - Stage determines treatment
- **Treatment**
  - In NSCLC, surgery is the cornerstone of treatment
- **Prognostic / Treatment factors**
  - Performance status (ECOG 0-4)
  - Weight loss (<5-10%)
  - Age/comorbidity
    - Pulmonary
    - Cardiac

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## First-line Treatment for Metastatic NSCLC

- ***Palliative Platinum-based chemotherapy***
- Adenocarcinoma – Cisplatin/Pemetrexed for PS 0-1; other options are available
- Squamous Cell – Carboplatin/Paclitaxel or Carboplatin/Gemcitabine for PS 0-2; other options are available
- Large Cell – Carboplatin/Paclitaxel/Bevacizumab or Carboplatin/Pemetrexed
- “Maintenance” pemetrexed chemotherapy for non-squamous (Paz-Ares et al. 2013)
  - Progression free survival = 4.3mos v. 2.6 mos

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## Molecular Targeted Therapy

- **Sensitizing EGFR** (epidermal growth factor receptor) mutation
  - **1<sup>st</sup> Generation**
    - Erlotinib
    - Gefitinib
  - **2<sup>nd</sup> Generation**
    - Afatinib
  - T790M mutant EGFR



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## EGFR TKI Therapy Side Effects

### Most Common

- Diarrhea
- Rash,
- Dry skin
- Dyspnea
- Cough
- Nail toxicity
- Paronychia

### Less Common

- Nausea
- Decreased  
Appetite
- Stomatitis
- Elevated LFTs
- Hypokalemia

*\*See erlotinib, gefitinib, afatinib package inserts\**

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# EGFR TKI Therapy Side Effects

## Serious Side Effects

- Interstitial Lung Disease/ Pneumonitis
- QTc interval prolongation
- Cardiomyopathy
- Embryo-fetal toxicity
- VTE

*\*See erlotinib, gefitinib, afatinib package inserts*

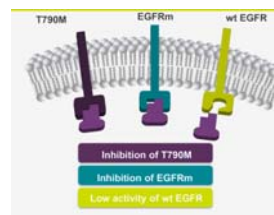


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# T790 Mutation Drugs

- T790 mutation is found on exon 20
- Indicates resistance to EGFR TK Inhibitors
- Median time to resistance of EGFR ~ 14 mos.
- New Drugs
  - Osimertinib
  - Rociletinib (not yet FDA approved)



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## T790m Therapy Side Effects

- [Same as other EGFR TKI]
  - Diarrhea
  - Rash
  - Dry Skin
  - Stomach upset: Nausea
  - Constipation
  - Decreased Appetite
- Cardiac Toxicities
- Hyperglycemia (with rociletinib)

*\*see osimertinib package insert\**

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## Molecular Targeted Therapy

### ALK (anaplastic lymphoma kinase) mutation

- **1<sup>st</sup> Generation**
  - Crizotinib
- **2<sup>nd</sup> Generation**
  - Ceritinib
  - Alectinib

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# ALK Therapy Side Effects

## ■ Most Common

- Vision Disorders
- Diarrhea
- Fatigue
- N/V, Constipation, Abdominal pain
- Edema
- Myalgia
- Elevated LFTs
- Cough
- Rash
- Headache

*\*See crizotinib, ceritinib, alectinib package inserts\**

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# ALK Therapy Side Effects (cont.)

## ■ Serious Side Effects

- Interstitial Lung Disease/ Pneumonitis
- Hepatotoxicity
- Bradycardia
- Severe Myalgia
- Embryo-fetal toxicity

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## Molecular Targeted Therapy Investigational Studies

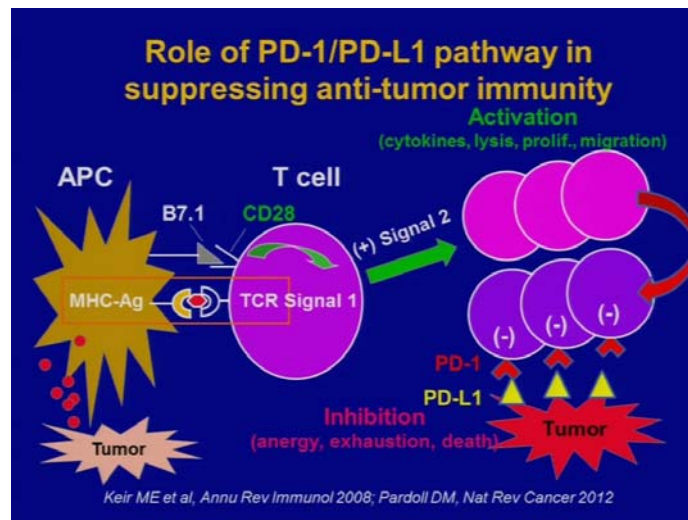
- **ROS1** – crizotinib approved 03/11/16
- **cMET/ RET** – testing crizotinib
- **KRAS** – no targeted therapy available
- **BRAF** – compassionate use BRAF inhibitors?

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## Immunotherapy



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## Anti PD-L1 Drugs

- Indicated *after* the use of platinum-based chemotherapy
  - **Pembrolizumab**
    - (PDL1 positivity required)
  - **Nivolumab**

*\*caution use with autoimmune disorders\**

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## Anti PD-L1 Drug Side Effects

### Most Common

- Malaise / Fatigue
- Low grade fever
- M/S pain
- Decreased appetite
- Cough
- Constipation
- Enlarged lymph nodes
- Elevated LFTs

*\*See pembrolizumab and nivolumab package inserts\**

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## Anti PD-L1 Drug Side Effects (cont.)

### Serious Side Effects

- Pneumonitis
- Immune-mediated
  - Colitis
  - Hepatitis
  - Nephritis
  - Renal Dysfunction / Adrenal Insufficiency
  - Rash
  - Encephalitis
- Embryofetal toxicity
- Serious: Interstitial lung disease; colitis; "...itis"

*\*See pembrolizumab and nivolumab package inserts\**

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## Current Investigations with Immunotherapies

- Small Cell Lung Cancer
- 1<sup>st</sup> line therapy for lung cancer
- Combination with chemotherapy
- Combination with 2 different immunotherapy blockades
  - (e.g. PDL1 + CTLA4)

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## Monoclonal Antibodies

- **VEGF** (vascular endothelial growth factor)
  - **Bevacizumab**
    - Only FDA approved with Carboplatin / Paclitaxel chemotherapy for 1<sup>st</sup> line treatment of Adenocarcinoma
      - *Difference in overall survival*
- **Necitumumab** – 1<sup>st</sup> line therapy with Cisplatin / Gemcitabine for Metastatic Squamous Cell (only)
- **Ramucirumab** – [VEGFR-2] FDA approved with Docetaxel 2<sup>nd</sup> line therapy
- **Ipilimumab** – under investigation

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## Palliative Care

- **Palliative care means more than Hospice**
  - ***Meticulous attention to:***
    - Symptom control
    - Pulmonary symptoms
    - Pain
    - Social support
    - Family/Caregiver needs

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# Palliative Care and Survival

- **Temel et al (2010)** *Early palliative care for patients with metastatic non-small-cell lung cancer*
  - Increased QoL
  - Decreased depression
  - Decreased EOL hosp. admissions
  - INCREASED SURVIVAL (11.6 mos. vs. 8.9 mos.)
- **Greer et al (2012)** *Effect of early palliative care on chemotherapy use and EOL care in pts. with metastatic NSCLC*
  - No difference between groups in # of chemo cycles
  - Optimized timing of final chemo cycle and smoother transition to hospice = good death
- **Nipp et al (2016)** *Age & Gender moderate the impact of early palliative care in metastatic NSCLC*
  - Males & younger pts. <65 years had increased QoL and Mood

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# NCCN Guidelines

## Guidelines to Wellness

- Anxiety/Depression
- Cognitive Function
- Fatigue
- Sleep Disorders
- Chronic pain
- Sexual Dysfunction

- Surveillance recommendations to guide f/u care



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# THANK YOU TEAM

- ***It takes a Village...***

- Nurses: RN/CNP/CNS
- Medical Oncologists
- Radiation Oncologists
- Thoracic Surgeons
- Radiologists
- Pathologists
- Molecular biologists
- Pharmacists
- Social Workers
- Hospice staff



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