Lung Cancer

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Objectives

- Define major risk factors for the development of lung cancer
- Describe the role of driver mutation status in determining treatment options
- Discuss general treatment options for patients with early stage and metastatic lung cancers

Lecture Outline

- Introduction
- Risk Factors
- Diagnosis
- Treatment Options
- Concluding Remarks

Incidence

- Leading cause of cancer-related death for men and women
- Second most common cancer diagnosis for both men and women
- Leading cancer diagnosis (1.8 million/year) and cancer-related cause of death worldwide

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2017 Estimates

Estimated New Cases

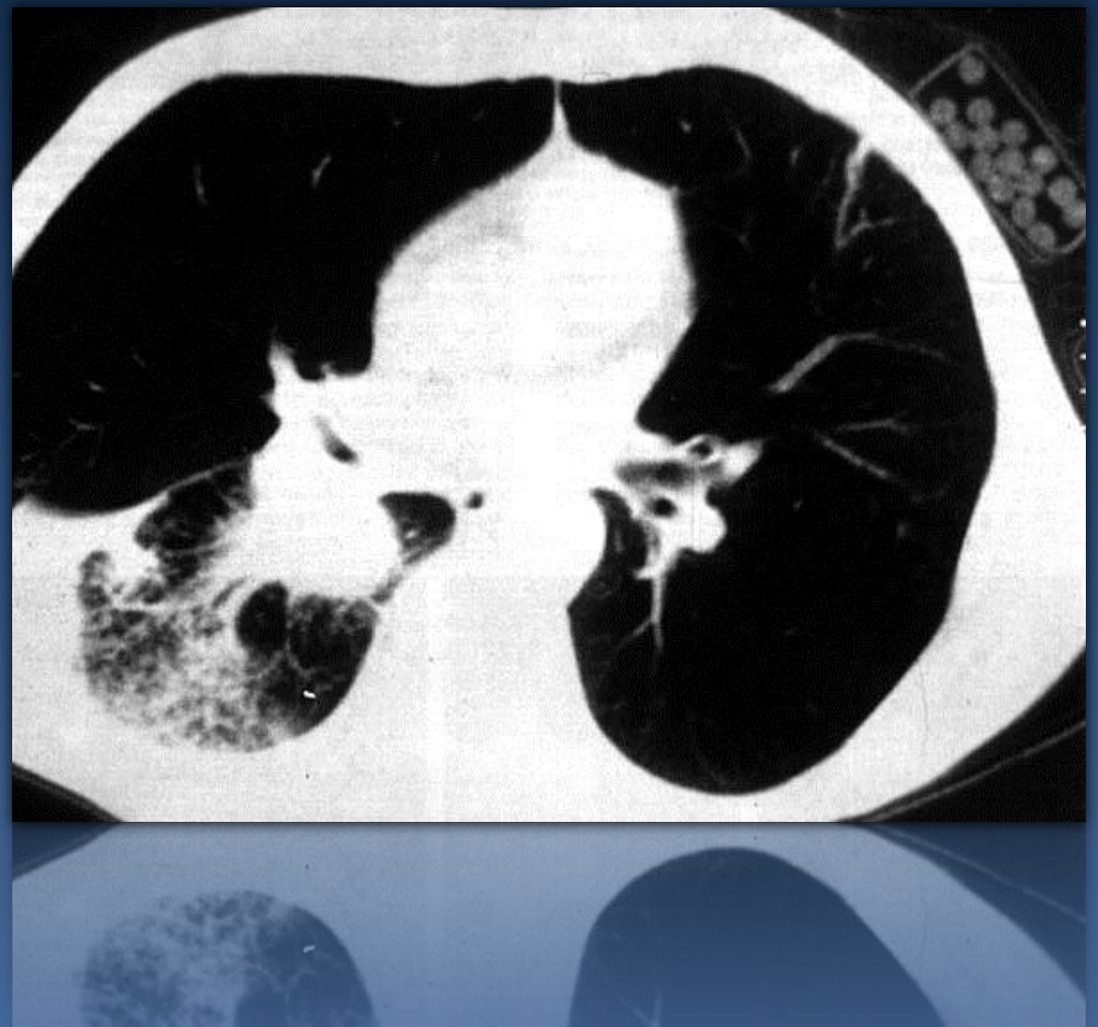
Male			Female		
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All sites	**836,150**	**100%**	**All sites**	**852,630**	**100%**

Estimated Deaths

Male			Female		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All sites	**318,420**	**100%**	**All sites**	**282,500**	**100%**

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

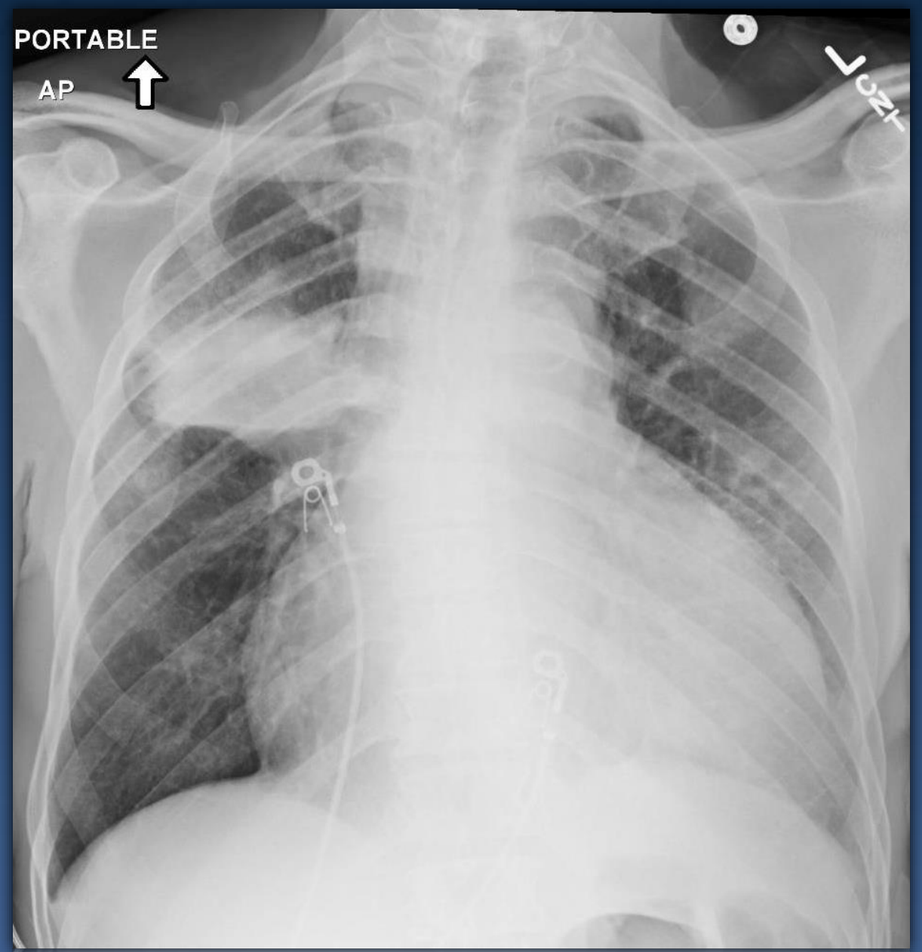
Risk Factors



- Smoking - #1 cause
- Radiation therapy
- Environmental toxins
- Pulmonary fibrosis
- HIV infection
- Genetic factors
- Alcohol
- Dietary factors

Diagnosis

- Imaging
  - CXR - gets the ball rolling
  - CT with estimation of cancer probability
  - To PET or not to PET?



Diagnosis

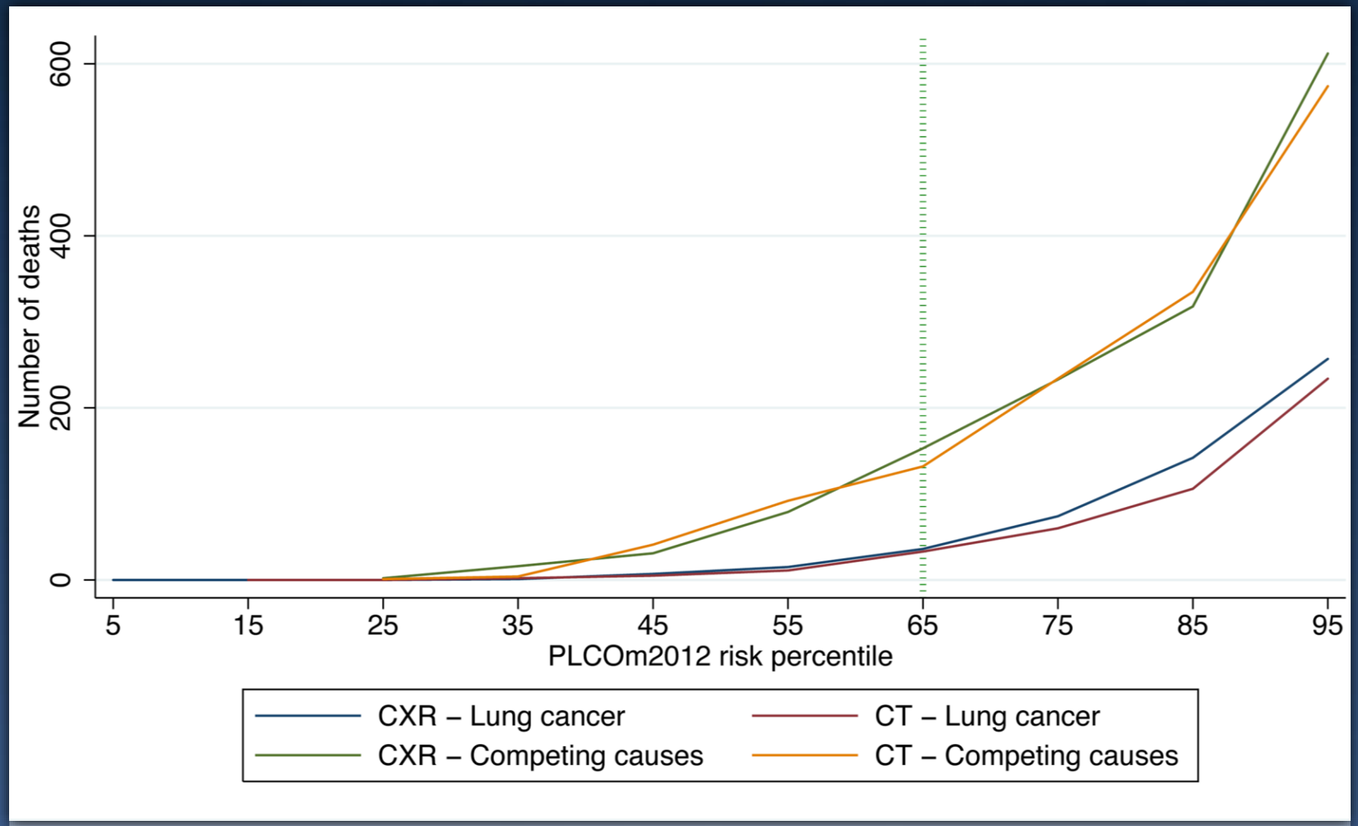
- CT imaging
  - Standard imaging modality for every case of suspected lung cancer
  - IV contrast preferred - helps define mediastinal anatomy, invasion from primary tumor, potentially involved lymph nodes

Brock University Malignancy Risk Calculator

https://doi.org/10.1371/journal.pmed.1001764

McWilliams A, Tammemagi MC, Mayo JR, et. al. *N Engl J Med*. 2013 Sep 5;369(10):910-9. doi:10.1056/NEJMoa1214726

- Calculates risk of cancer based on a statistical model that includes age, gender, co-morbidities, size of mass, and characteristics of mass (spiculated, single vs multiple, etc.)
- Provides information that guides approach (monitor vs biopsy)



Diagnosis

- Imaging
  - To PET or not to PET?
    - May reveal occult metastatic disease
    - Reduces number of unnecessary thoracotomies but did not affect overall survival (Fischer B, et al; *N Engl J Med*. 2009;361(1):32)
    - Integrated PET/CT widely used, but no current consensus as to its use — *consider biopsy of suspected lesions in patients who may otherwise be resectable!*

Diagnosis

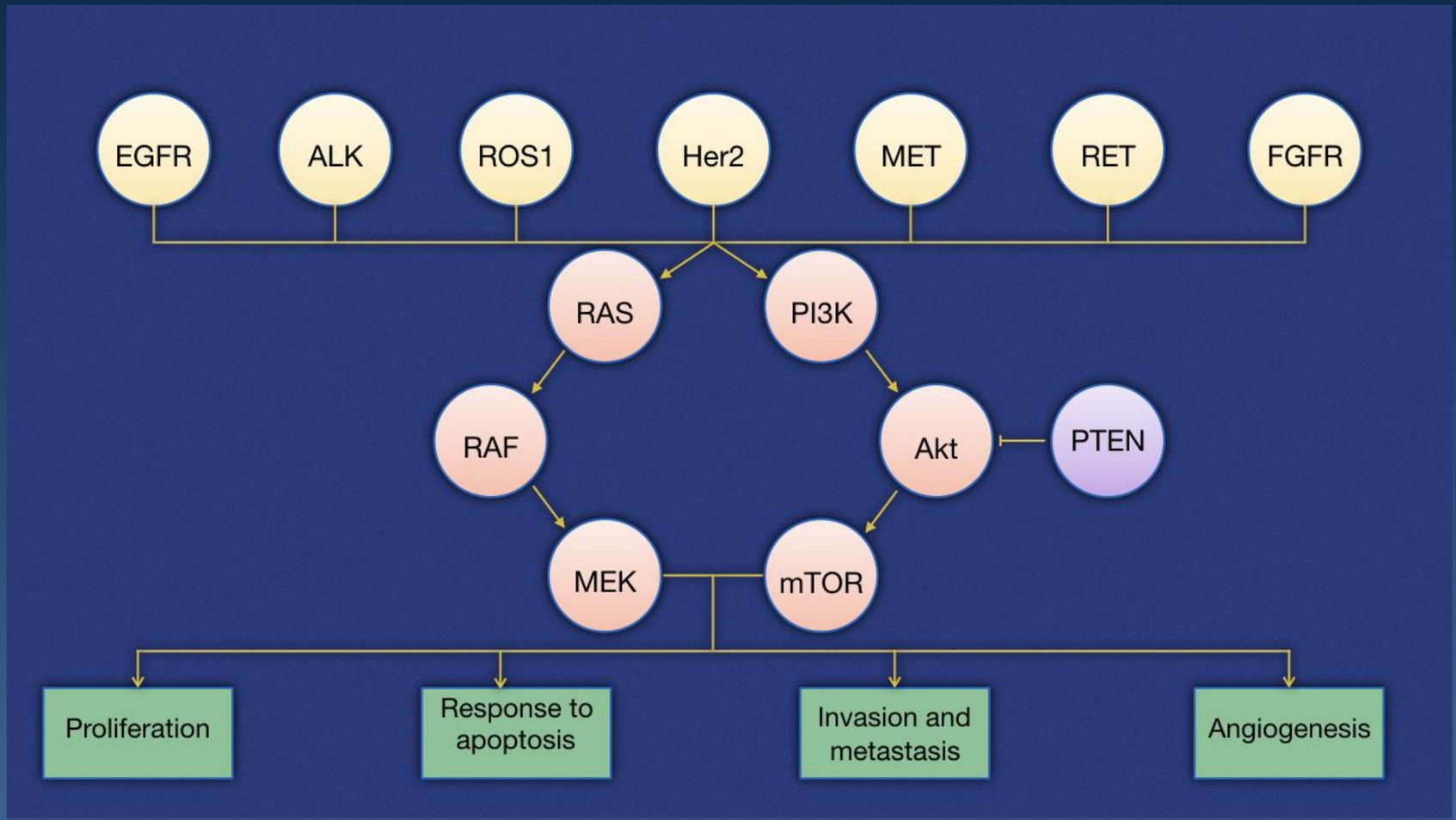
- Biopsy procedures
  - Needle (IR) — helpful for peripheral lesions, and some hilar/mediastinal nodes
  - Bronchoscopy ± EBUS
    - Brushings and transbronchial bx possible
    - Endobronchial ultrasound (EBUS) allows for bx of worrisome lymph nodes and some hilar/mediastinal masses (1º choice)
  - VATS/Mediastinoscopy — historical gold standard, increasingly relegated to second attempt after primary modalities fail

Diagnosis

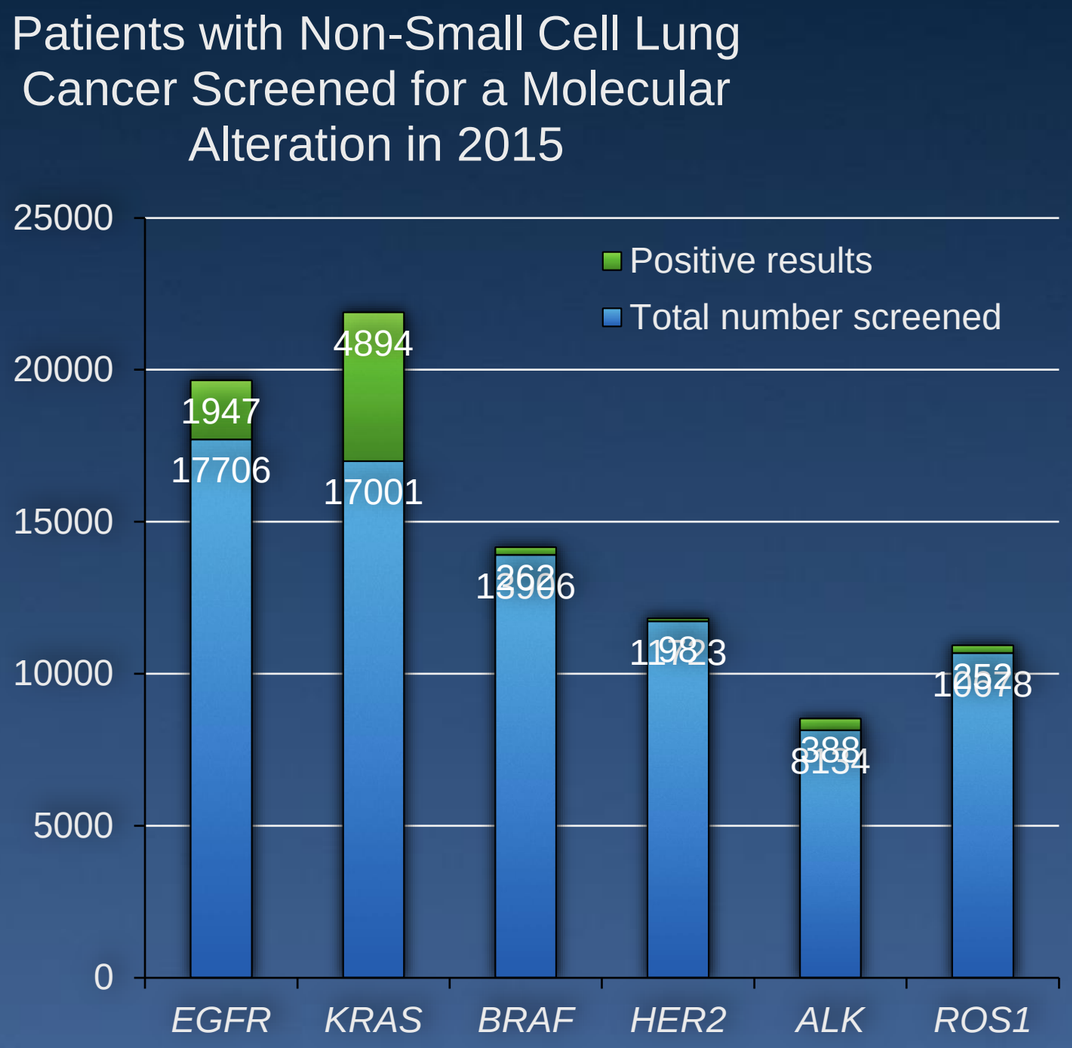
- Determination of driver mutation status, immune marker status
  - EGFR, ALK, ROS-1; PD-1/PD-L1

Newer Approaches in NSCLC

- “Driver mutation” — occur in cancer cells with mutations in genes encoding for proteins critical to cell growth and survival
  - Typically not found in the germ line (normal) cells, thus allows for targeting of malignant cells



Is Driver Mutation Status Helpful?



Barlesi F, Mazieres J, Merlio J-P, et al; *Lancet* 2016;387:1415-1426.

- French Cooperative Thoracic Intergroup Trial
  - 26,000 patients in 28 centers
  - A driver mutation was recorded ~50% of the time

Treatment Options

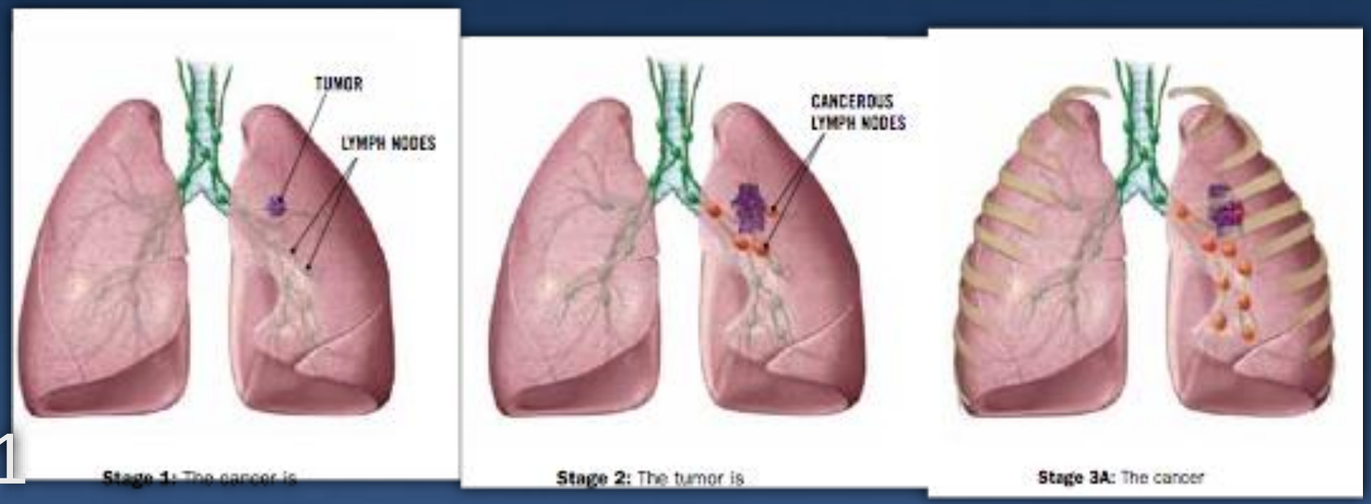
- Candidates for resection
- Management of Stage I and II Disease (“Early Stage”)
- Management of Stage III Disease
- Management of Stage IV Disease

Candidates for Resection

- SCLC managed with chemotherapy ± RT
- NSCLC may be managed with surgery
  - Anatomic considerations: limited to one lung, mediastinum uninvolved, no distant metastasis
  - Medical considerations: pulmonary function limitations, may be limited by concomitant disease

Candidates for Resection

- Stage I (no nodal involvement)
- Stage II (includes T1b patients, and patients with N1 disease)
- Stage IIIA (T1 or T2 with N2 disease, T3N1, T4 with N0 or N1 disease)



Stage 1: The cancer is small (no larger than 3 cm for stage 1A; up to 5 cm for stage 1B) and has not spread to the lymph nodes.

Stage 2: The tumor is up to 7 cm in diameter and may have spread to nearby lymph nodes.

Stage 3A: The cancer has started to extend into surrounding tissues and structures, such as the lining of the lung and chest wall, and has spread to lymph nodes on the same side of the chest as the tumor.

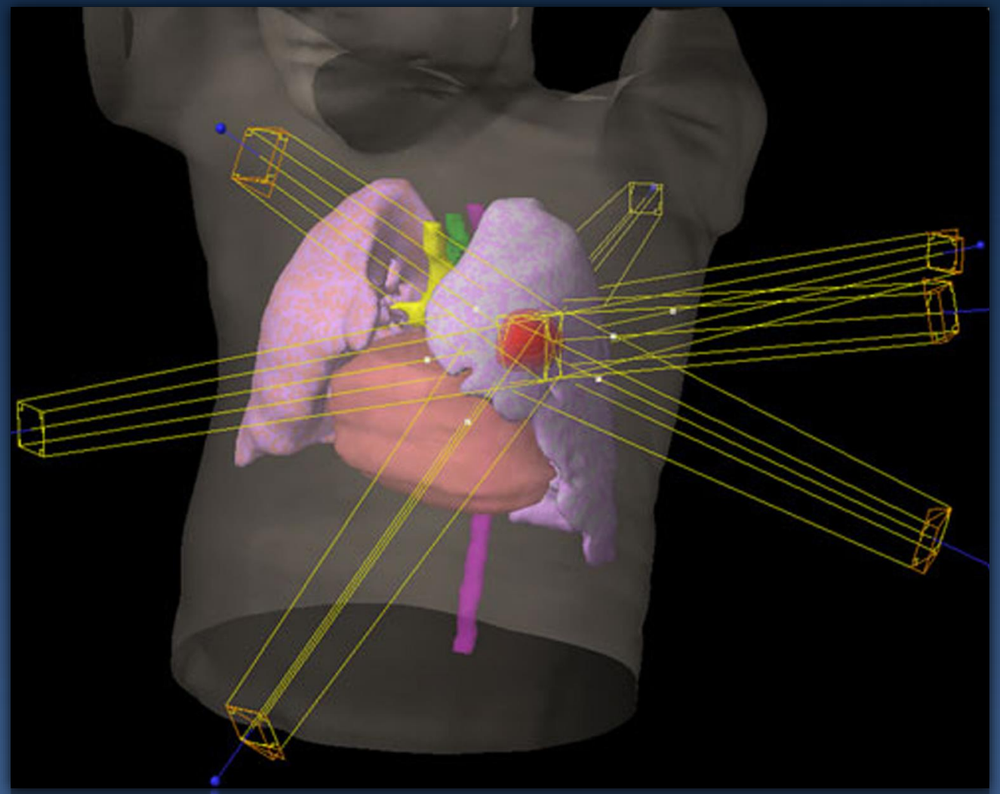
Choice of Surgery In Early Stage Disease

- Pre-operative evaluation essential
  - PFTs - patients with a preoperative FEV_1 in excess of 2 L (or >80% predicted) generally tolerate pneumonectomy, whereas those with a preoperative FEV_1 greater than 1.5 L tolerate lobectomy
  - DLCO - Retrospective studies: actual DLCO (% of the predicted value) and predicted post-op DLCO are most important predictors of mortality and postop complications (Liptay MJ, et al., *J Surg Oncol.* 2009;100(8):703)
  - Additional testing (exercise tolerance, ABG, others) as indicated

Choice of Surgery In Early Stage Disease

- Lobectomy - generally preferred over more limited procedure for peripheral lesions if goal is complete resection
- Pneumonectomy - proximal tumors. Sleeve resection may be needed
- Video-assisted thoracoscopy (VATS) - may be reasonable option to open procedure
  - Lower operative morbidity and faster recovery
  - Most trials of adequacy vs open thoracotomy are single institution retrospective studies and small prospective trials

Radiation Therapy in Early Stage Disease



- SBRT (stereotactic body radiation therapy) - delivers focused, discrete RT in single or multiple large dose using multiple convergent beams
- Multiple series demonstrate local control rate at >90% and survival rates similar to surgery

Systemic Therapy in Early Stage Disease

- “Platinum doublet” therapy (Cisplatin plus additional agent) standard of care for adjuvant therapy in Stage II and selected Stage Ib patients
  - In non-squamous histology - pemextrexed
  - In squamous histology - taxanes, vinorelbine, or gemcitabine
- No current role for molecularly targeted therapies

Treatment of Early Stage NSCLC

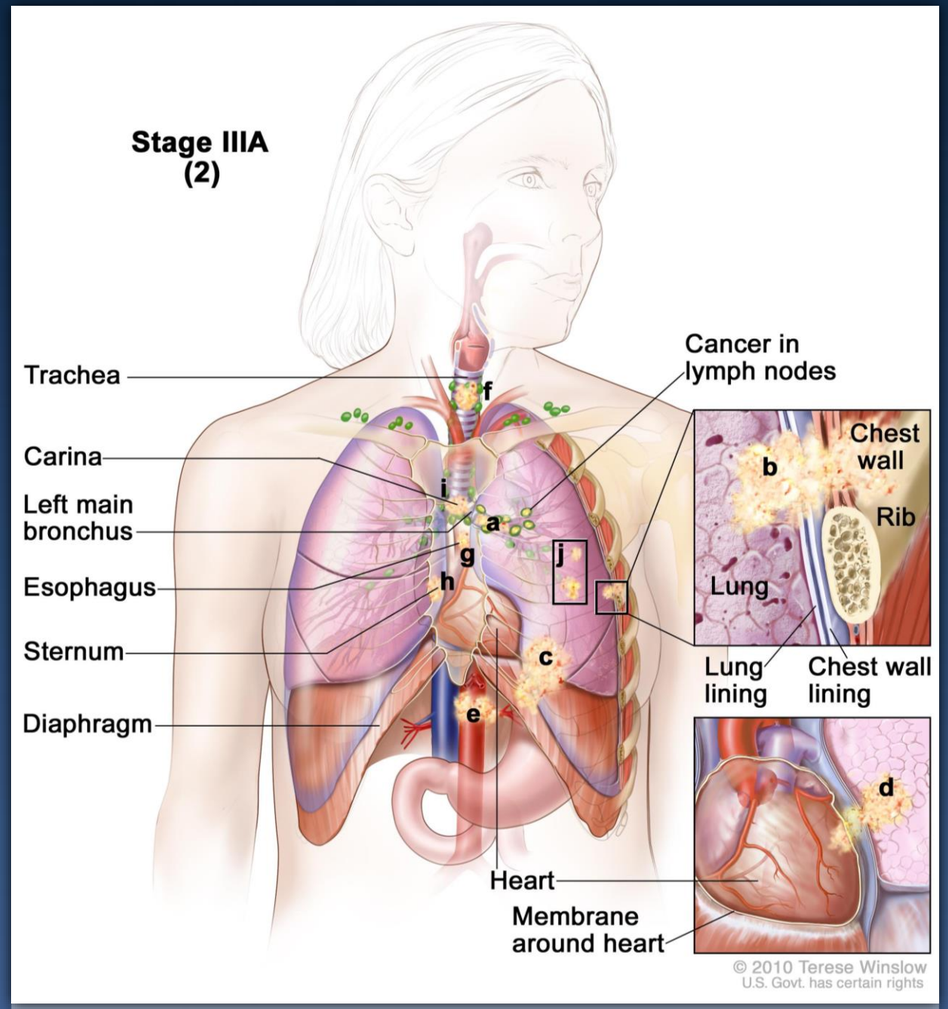
- Surgery (lobectomy) or SBRT
- Patients with Stage II disease (and some Stage Ib patients) receive adjuvant systemic therapy for four cycles
- Patients should be offered participation in clinical trials if interested

Management of Stage III Disease

- This is a heterogenous population and treatment must address the patient and the problem
- The new staging system (8th edition) now includes patients with primary tumor extension into extrapulmonary structures (T3 or T4) or mediastinal lymph nodes (N2 or N3) without distant metastasis. It also includes tumors >5 cm in size with hilar, intrapulmonary, or peribronchial lymph node involvement (T3N1) or tumors >7 cm (T4) regardless of node status

Management of Stage III Disease

- T3N1
  - Surgery if resection is feasible, followed by chemo.
  - If surgery not feasible, combination chemo/RT
- Most other presentations will require chemo/RT in the frontline setting



Management of Metastatic Disease

- Questions…
  - Immune markers present?
  - Driver mutation present?
  - Goals of care/treatment?

Immunotherapy in Lung Cancer???

- For many years, bronchogenic carcinoma not considered immunogenic
- Phase I study of nivolumab in previously treated NSCLC (Raez LE, et al. *Clin.Med. Res.* 2005. 3:221-228))
  - Nivolumab - fully human PD-1 monoclonal antibody
  - Overall response 18%, OS 9.9 months, 1-year survival 42%

Immunotherapy in Lung Cancer???

- Phase 2 study of nivolumab in refractory squamous cell NSCLC demonstrated 14.5% overall response rate (Topalian SL, Hodi FS, Brahmer JR. *New Engl Jour Med* 2012; 366:2443)
  - Durable responses noted, lasting several months
  - Most patients treated with conventional therapy who respond have a response duration of a few weeks

Immunotherapy in Lung Cancer???

http://www.medscape.org/viewarticle/844988

CheckMate 017: Phase 3 Trial of Nivolumab vs Docetaxel in Squamous Cell NSCLC

272 pts with squamous cell NSCLC with PD during or after 1st-line chemotherapy

- Nivolumab 3 mg/kg q2W
- Docetaxel 75 mg/m² q3W

Primary end point: overall survival
Secondary end points: ORR, PFS, PROs, efficacy based on tumor PD-L1 expression, safety

Parameter	Nivolumab (n = 135)	Docetaxel (n = 137)	*P* Value
Median OS, mo	9.2	6.0	< .0001
• HR (95% CI)	0.59 (0.44-0.79)		
• 1-y OS, %	42	24	
ORR, %	20	9	.0008
Median PFS, mo	3.5	2.8	< .0001
• HR (95% CI)	0.62 (0.47-0.81)		

PRO = patient reported outcomes

Brahmer J, et al. *N Engl J Med.* 2015 May 31. [Epub ahead of print][15]

CheckMate 057: Phase 3 Trial of Nivolumab vs Docetaxel in Nonsquamous Cell NSCLC

582 pts with advanced nonsquamous cell NSCLC with failure of platinum doublet

- Nivolumab 3 mg/kg Q2W
- Docetaxel 75 mg/m² Q3W

Primary end point: overall survival
Secondary end points: ORR, PFS, efficacy based on tumor PD-L1 expression, safety

Parameter	Nivolumab (n = 292)	Docetaxel (n = 290)	*P* Value
Median OS, mo	12.2	9.4	.0015
• HR (95% CI)	0.73 (0.59-0.89)		
• 1-y OS, %	51	39	
ORR, %	19	12	.0246
Median PFS, mo	2.3	4.2	NS
• HR (95% CI)	0.92 (0.77-1.11)		

Paz-Ares L, et al. *J Clin Oncol*. 2015;33. Abstract LBA109.[17]

Improved response and overall survival vs docetaxel

Immunotherapy in Lung Cancer???

- As a result of this data, the US Food and Drug Administration granted approval on March 4, 2015 of nivolumab for the treatment of patients with advanced squamous NSCLC with progression on or after platinum-based chemotherapy

Immunotherapy in Lung Cancer???

- Pembrolizumab→KEYNOTE 001 Trial (Geron EB, et al.; *N Engl J Med* 2015; 372:2018-2028)
  - Phase I trial of 495 patients receiving pembrolizumab at a dose of either 2 mg/kg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks
  - Assigned to either a training group (182 patients) or a validation group (313 patients)
  - PD-L1 expression in tumor samples assessed using immunohistochemical analysis, with results reported as the percentage of neoplastic cells with staining for membranous PD-L1 (proportion score)

Immunotherapy in Lung Cancer???

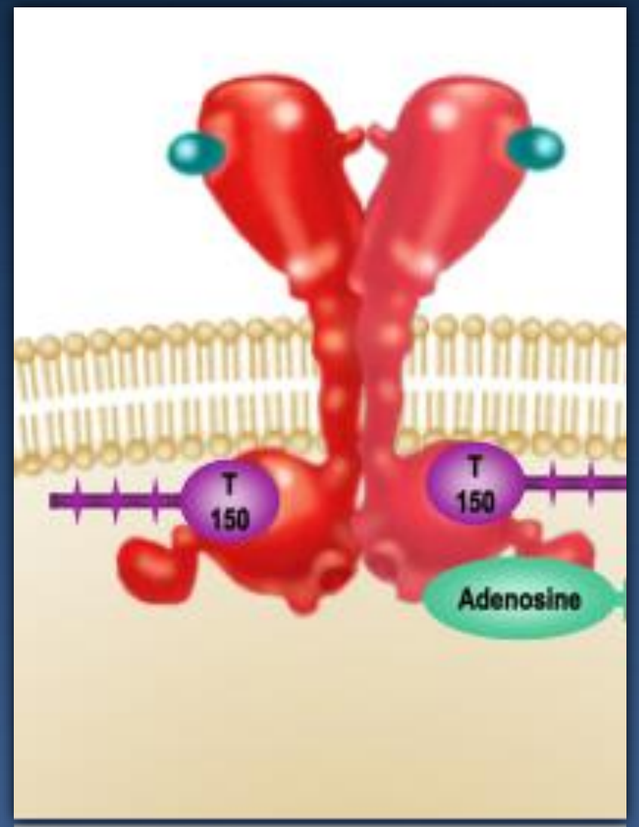
- KEYNOTE 001-Results (all patients on treatment) (Geron EB, et al.; *N Engl J Med* 2015; 372:2018-2028)
  - Objective response rate 19.4%
  - Median duration of response 12.5 months
  - Median duration of progression-free survival 3.7 months
  - Median duration of overall survival 12 months
  - PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy→ORR in that group was 45.2% median overall survival not reached at time of data analysis

Immunotherapy in Lung Cancer???

- Toxicities to PD-1/PD-L1 therapies
  - General: fatigue, rash, pruritis, myalgias, loss of appetite
  - On occasion: colitis, thyroiditis, elevation of liver transaminases, autoimmune disorders (GBS, transverse myelitis, others)
  - Pseudo-progression: can cause increase in pain, neurological changes

Newer Approaches in NSCLC

- Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors
  - Erlotinib (Tarceva®)
  - Gefitinib (Iressa®)
  - Afatinib (Gilotrif®)



Epidermal Growth Factor Receptor

Newer Approaches in NSCLC

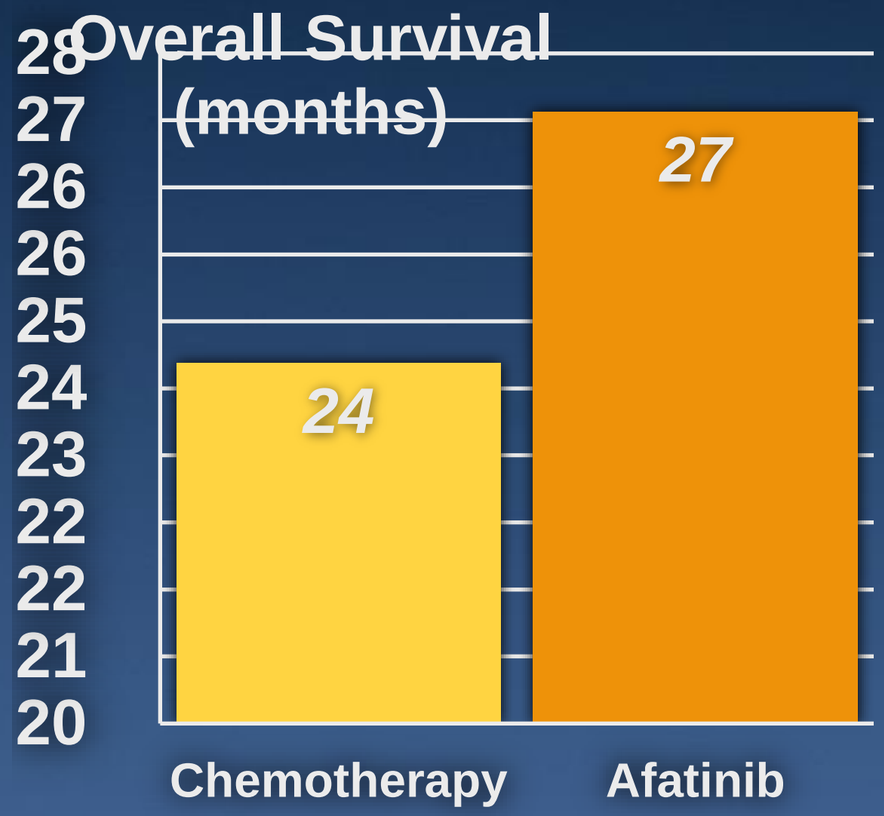
- Afatinib (Gilotrif®)
  - Irreversible EGFR-TKI, with specificity for the exon 19 deletion or the exon 21 (L858R) substitution mutation
  - Approved for use by FDA in July 2013

Newer Approaches in NSCLC

- LL3/LL6 Studies (Yang JCH et al.; *J Clin Oncol* 32:5s, 2014 [suppl; abstr 8004])
  - Two large studies comparing afatinib to chemotherapy
  - Pooled analysis of 631 patients randomized 2:1 to afatinib vs chemotherapy in patients with *EGFR*+ NSCLC, Stages III-B and IV

Newer Approaches in NSCLC

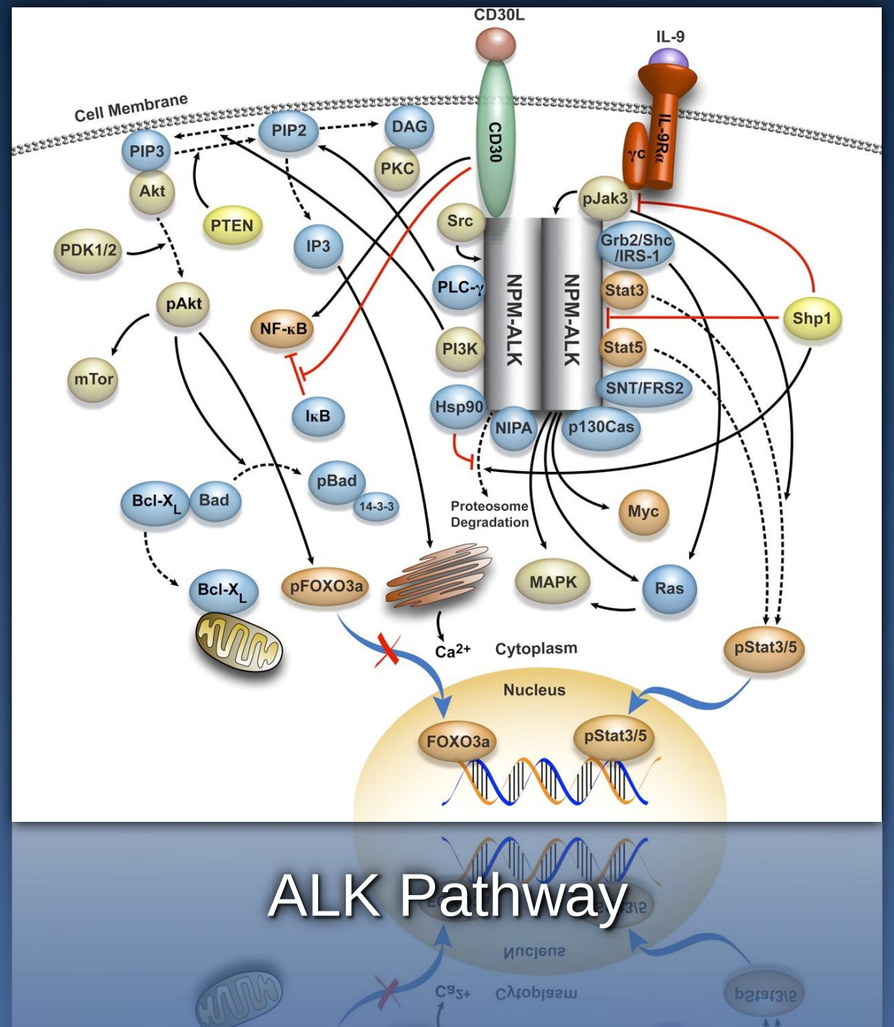
Yang JCH et al.; *J Clin Oncol* 32:5s, 2014 (suppl; abstr 8004)



- HR=0.81 [CI 0.66, 0.99; p=0.037]
- First study to demonstrate overall survival benefit for genotype-driven therapy vs chemotherapy in metastatic NSCLC

Newer Approaches in NSCLC

- Anaplastic lymphoma kinase (ALK) fusion oncogene tyrosine kinase inhibitors
  - Crizotinib (Xalkori®)
  - Ceritinib (Zykadia®)



ALK Pathway

Newer Approaches in NSCLC

- First-line crizotinib versus pemetrexed–cisplatin or pemetrexed–carboplatin in patients with advanced *ALK*-positive NSCLC (Mok T, et al.; *J Clin Oncol* 32:5s, 2014 suppl; abstr 8002)
  - 343 patients with previously untreated advanced non-squamous *ALK*-positive NSCLC randomized to crizotinib 250 mg po bid vs pemetrexed 500 mg/M^2 + either cisplatin 75 mg/M^2 or carboplatin AUC 5-6 all IV q 3 weeks for 6 or more cycles
  - Subsequent crossover to opposite arm permitted after primary response data completed

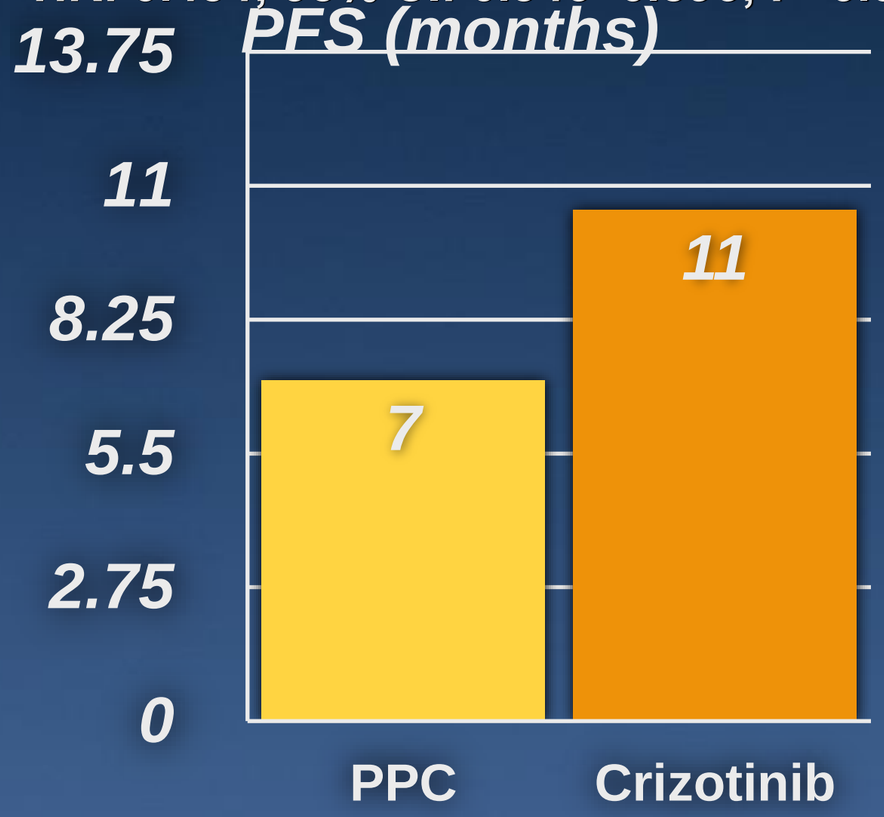
Newer Approaches in NSCLC

- First-line crizotinib versus pemetrexed–cisplatin or pemetrexed–carboplatin in patients with advanced *ALK*-positive NSCLC (Mok T, et al.; *J Clin Oncol* 32:5s, 2014 suppl; abstr 8002)
  - Arms matched for ethnicity, gender, performance status, incidence of brain metastases

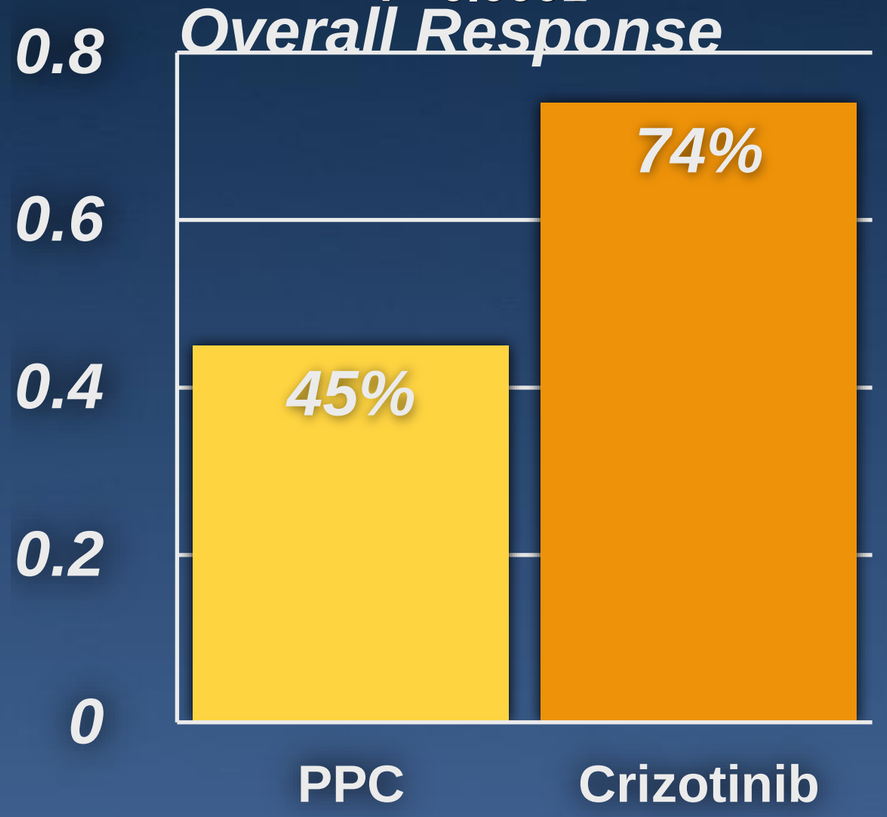
Newer Approaches in NSCLC

Mok T, et al.; *J Clin Oncol* 32:5s, 2014 suppl; abstr 8002

HR: 0.454; 95% CI: 0.346–0.596; P<0.0001



P<0.0001



Newer Approaches in NSCLC

- Ceritinib (Zykadia®)
  - 2nd generation *ALK* TKI 20 times more potent than crizotinib
  - Much enthusiasm for this agent based on the initial findings of the ASCEND-1 trial (Kim DW, et al. *J Clin Oncol* 32:5s, 2014; suppl; abstr 8003)
    - 255 *ALK*+ patients enrolled to expansion groups: ALKi pretreated; ALKi naive; non-NSCLC diseases
    - Dose of 750 mg/d orally based on Phase I data (the MTD)

Newer Approaches in NSCLC

(Kim DW, et al. *J Clin Oncol* 32:5s, 2014; suppl; abstr 8003)

Endpoint	ALKi previous treatment N=121	ALK naive N=59	All N=180
Overall Response Rate n (%) [95% CI]	67 (55.4%) [46.1, 64.4]	41 (69.5%) [56.1, 80.8]	108 (60.0%) [52.4, 67.2]
Duration of Response (Median [95% CI])	7.4 mos [5.4, 10.1]	rate at 12 mos: 71.1% [49.8, 84.6]	9.7 mos [6.9, 11.4]
Time to First Response (Median [min, max])	6.1 wks [4.6, 24.1]	6.1 wks [3.0, 24.1]	6.1 wks [3.0, 24.1]
Progression-Free Survival (Median [95% CI])	6.9 mos [5.4, 8.7]	rate at 12 mos: 58.1% [41.6, 71.5]	7.0 mos [6.2, 10.1]

Newer Approaches in NSCLC

- Based on this information, the current approach in metastatic NSCLC is to include driver mutation status in treatment planning
- 3 groups…
  - Driver mutation absent
  - Driver mutation status unknown
  - Driver mutation present

Newer Approaches in NSCLC

- Driver mutation absent…
  - Combination chemotherapy is standard
  - Platinum doublets dominate, often combined with bevacizumab
  - Maintenance chemotherapy with a single agent often utilized (pemetrexed) on completion of combination tx in non-squamous histology

Newer Approaches in NSCLC

- Driver mutation status unknown…
  - Combination chemotherapy as long as status is unknown
  - If data becomes available, the results are incorporated into treatment when feasible

Newer Approaches in NSCLC

- Driver mutation present…
  - EGFR mutation positive—treatment with an EGFR TKI (erlotinib, gefitinib, afatinib) indicated in the frontline
    - Improves progression-free survival compared to chemotherapy
  - ALK fusion oncogene positive—treatment with an ALK TKI (crizotinib, ceritinib) indicated in the frontline
    - Higher response rate compared to chemotherapy

Newer Approaches in NSCLC

- New treatments have added several options to armamentarium in metastatic disease
- Several data sets demonstrating that palliative care team can improve quality of life scores and survival in metastatic NSCLC
  - Survival improved by ~30% by inclusion of palliative care team in addition to oncologic therapies (Temel JS, et al., *N Engl J Med.* 2010;363(8):733)

Concluding Remarks

- Define major risk factors for the development of lung cancer
  - Smoking, pulmonary fibrosis, EtOH use, others

Concluding Remarks

- Describe the role of driver mutation status in determining treatment options
  - 50% of patients on average had an actionable mutation
  - Used in setting of metastatic disease
  - May be combined with other modalities in the near future

Concluding Remarks

- Discuss general treatment options for patients with early stage and metastatic lung cancers
  - Goal of treatment in early stage disease is cure
  - Goal of treatment in advanced disease is disease-free survival
  - Goal of treatment in metastatic disease is palliative

things are changing quickly…

Stay Tuned!!!


Questions?