Genetic Testing and Targeted Therapies for Incurable Lung Cancer

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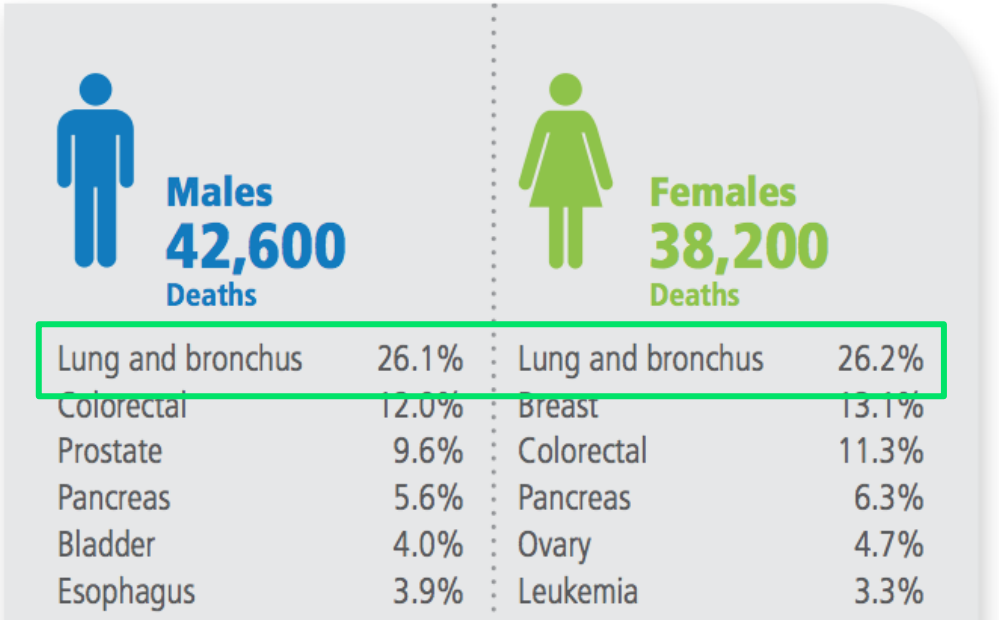
Presenter Disclosure

- **Faculty:** Craig Henry Harlos
- **Relationships with commercial interests:**
  - **None to declare**

Objectives

- Describe the major types of targetable mutations in lung cancer and their corresponding therapies
- Identify which patients are appropriate for genetic testing
- Recognize targeted therapy toxicities and how to manage them

The Impact of Lung Cancer in Canada

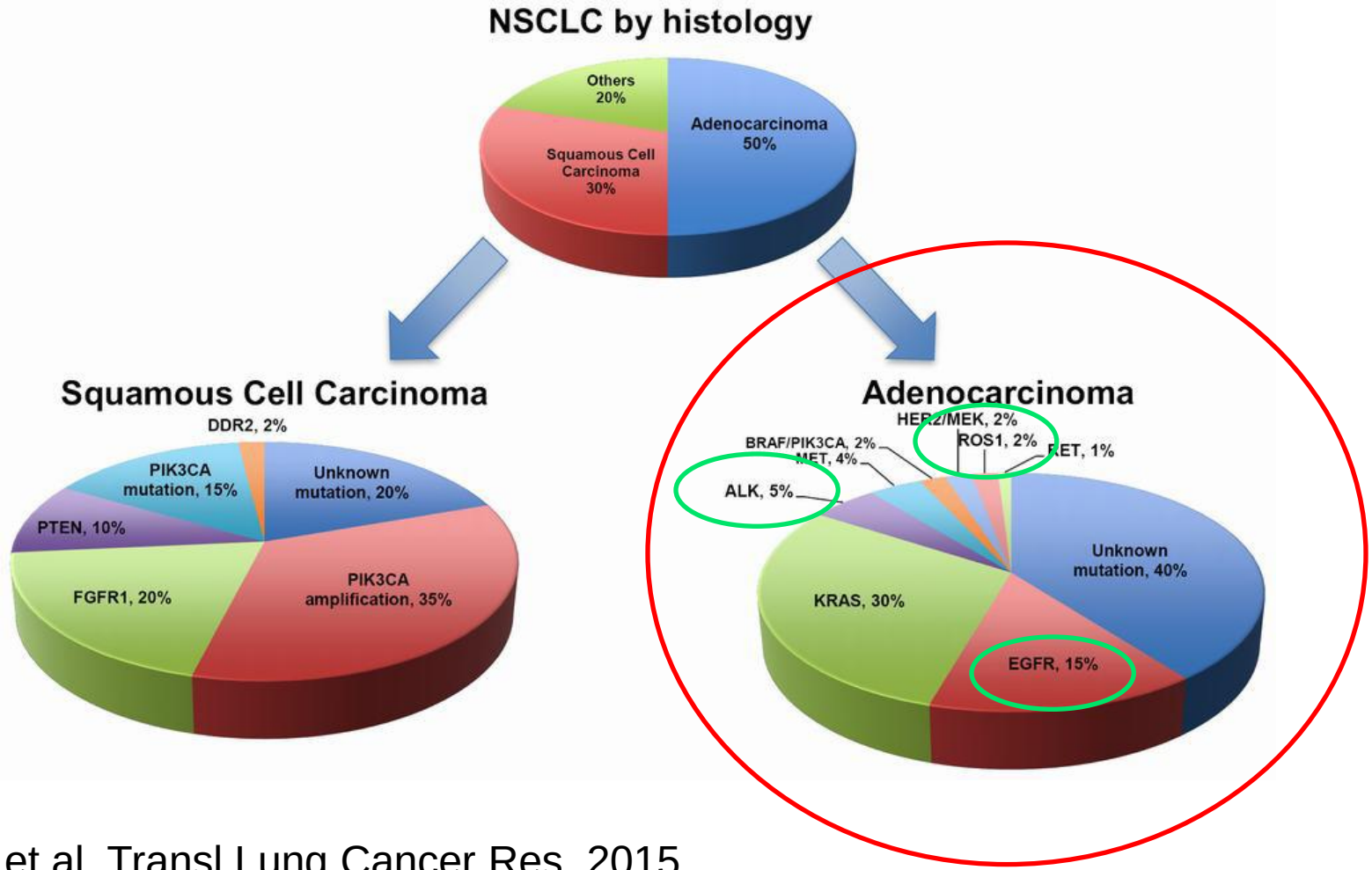


Males 42,600 Deaths		Females 38,200 Deaths	
Lung and bronchus	26.1%	Lung and bronchus	26.2%
Colorectal	12.0%	Breast	13.1%
Prostate	9.6%	Colorectal	11.3%
Pancreas	5.6%	Pancreas	6.3%
Bladder	4.0%	Ovary	4.7%
Esophagus	3.9%	Leukemia	3.3%

- 21,100 Canadians will die from lung cancer.
  - This represents 26% of all cancer deaths in 2017.
  - 14,400 men and 14,200 women will be diagnosed with lung cancer
  - On average, 58 Canadians will die from lung cancer every day.

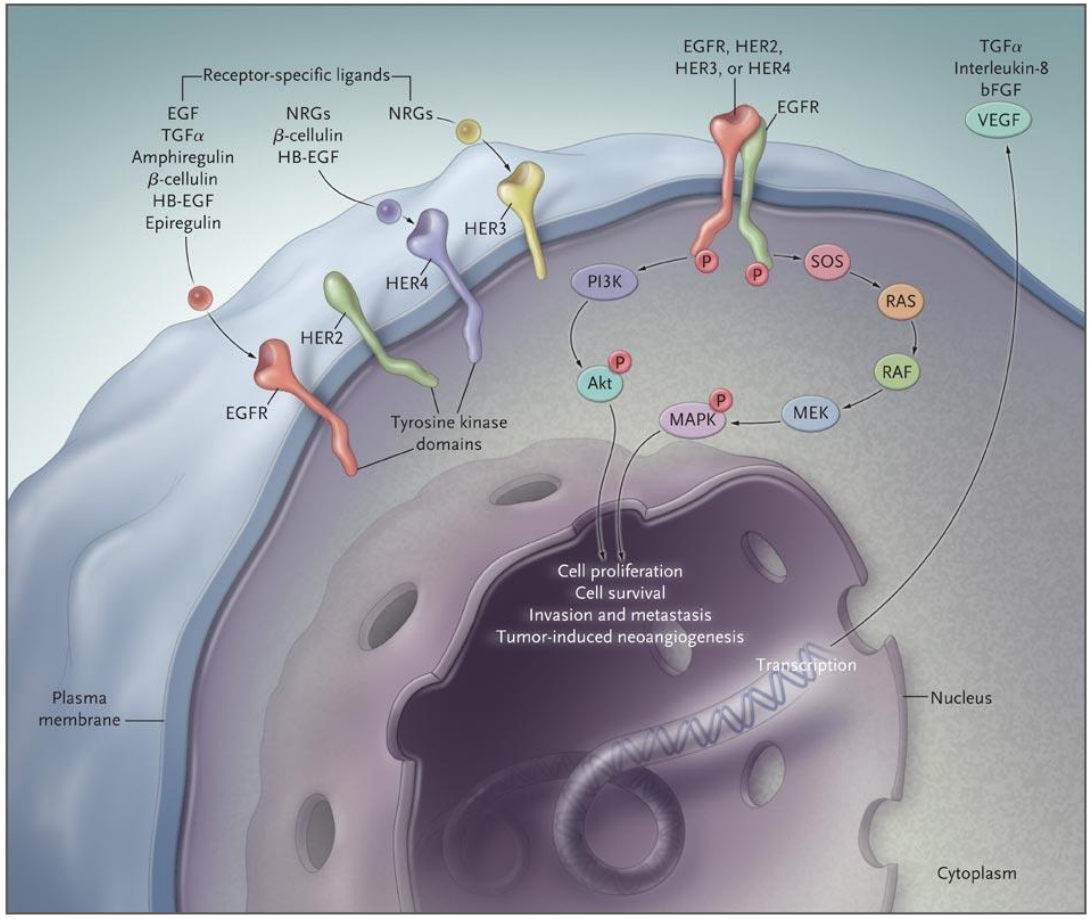
Canadian Cancer Statistics 2017

Molecular landscape of Lung cancer



Chan, BA et al. Transl Lung Cancer Res. 2015

Epidermal Growth Factor Receptor



Ciardiello F, Tortora G. N Engl J Med. 2008

EGFR mutations in lung cancer

- Almost exclusively in non-squamous NSCLC
- The most common mutations are exon 19 deletions (60%) and L858R missense substitutions on exon 21 (35%)
- Exon 20 T790M mutation is associated with resistance to TKI therapy
- Mutually exclusive with other mutations eg. ALK fusion, ROS1, KRAS
- Enriched in Asian populations, female, non-smokers (up to 50%)

EGFR Tyrosine Kinase Inhibitors

- First Generation
  - Reversibly inhibits EGFR tyrosine kinase activity
  - Gefitinib
  - Erlotinib
- Second Generation
  - Covalently and irreversibly binds to the intracellular tyrosine kinase domain of EGFR
  - Afatinib
  - Dacomitinib
- Third Generation
  - Irreversible EGFR tyrosine kinase inhibitor which binds to mutant forms of EGFR, including T790M, L858R, and exon 19 deletion
  - Osimertinib

Trials for first line therapy in advanced NSCLC

Table 1 Phase III Trials comparing EGFR-inhibitors to chemotherapy in advanced stage IIIB/IV NSCLC

Trial [year] (Ref)	Patient selection	Targeted therapy (TT)	Comparator (C)	Median PFS TT *vs.* C (mo.)	HR	P value
First-line EGFR TKI versus chemotherapy						
IPASS [2009] (39,40)	n=1,217, clinical, non/light smokers, Adc, 60% EGFR mutant (Asia)	Gefitinib	Carboplatin; Paclitaxel	9.8 *vs.* 6.4	0.48	≤0.001
First-SIGNAL [2012] (41)	n=309, clinical, never smokers, Adc, 44% EGFR mutant	Gefitinib	Cisplatin; Gemcitabine	5.8 *vs.* 6.4	1.198	0.138
WJTOG3405 [2010] (42)	n=172, molecular EGFR mutant	Gefitinib	Cisplatin; Docetaxel	9.2 *vs.* 6.3	0.489	<0.0001
NEJSG [2010] (43)	n=230, molecular EGFR mutant	Gefitinib	Carboplatin; Paclitaxel	10.8 *vs.* 5.4	0.30	<0.001
OPTIMAL [2011] (44)	n=154, molecular EGFR mutant, 88% Adc	Erlotinib	Carboplatin; Gemcitabine	13.1 *vs.* 4.6	0.16	<0.0001
EURTAC [2012] (45)	n=174, molecular EGFR mutant	Erlotinib	Platinum doublet	9.7 *vs.* 5.2	0.37	<0.0001
LUX-Lung3 [2013] (46)	n=345, molecular EGFR mutant Adc	Afatinib	Cisplatin; Pemetrexed	11.1 *vs.* 6.9	0.58	0.001
LUX-Lung6 [2014] (47)	n=364, molecular EGFR mutant Adc	Afatinib	Cisplatin; Gemcitabine	11.0 *vs.* 5.6	0.28	<0.0001

Chan, BA et al. Transl Lung Cancer Res. 2015

EGFR Tyrosine Kinase Inhibitors

- Results from meta-analyses:
  - Significantly improved PFS with EGFR TKIs vs. chemotherapy
    - **HR 0.37**; 95% CI, 0.32 to 0.41; P<0.001),
  - No difference in OS
    - **HR 1.01**; 95% CI, 0.86 to 1.19; P.88)
  - Greater benefit in Exon 19 mutations, never smokers, women
  - Quality of life and adverse event rates favor EGFR TKIs

Lee CK et al. J Clin Oncol. 2015

Greenhalgh J et al. Cochrane Database Syst Rev. 2016

EGFR Tyrosine Kinase Inhibitors

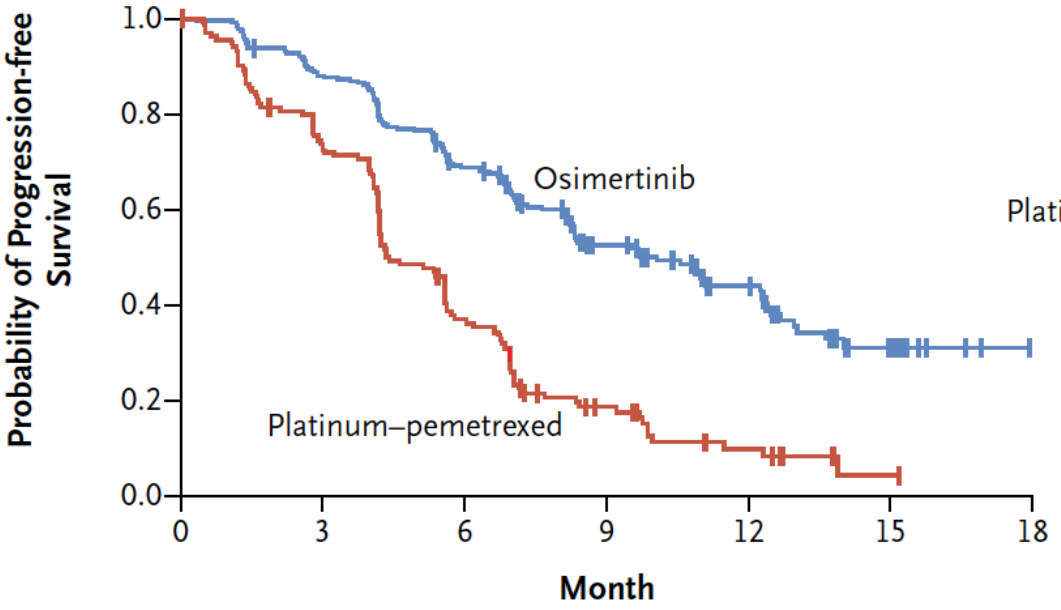
- Despite high initial response rate, resistance invariably develops to first line EGFR TKIs
- Resistance mechanisms include secondary mutations, alternate pathways eg amplification of MET, transformation to SCLC
- T790M mutations occur in 50-60% of cases

Osimertinib

- Osimertinib is selective for both EGFR-TKI sensitizing and T790M resistance mutations
- Presence of T790M mutation must be confirmed by repeat biopsy or circulating tumor (ct) DNA
- AURA3 (Mok et al. NEJM 2016)
  - T790M-positive advanced NSCLC, disease progression after first-line EGFR-TKI therapy, osimertinib vs. platinum doublet
  - PFS significantly improved (**10.1 months vs. 4.4 months; hazard ratio; 0.30**)
  - Response rate **71% vs. 31%**
  - OS data not yet mature

Osimertinib

A **Patients in Intention-to-Treat Population**



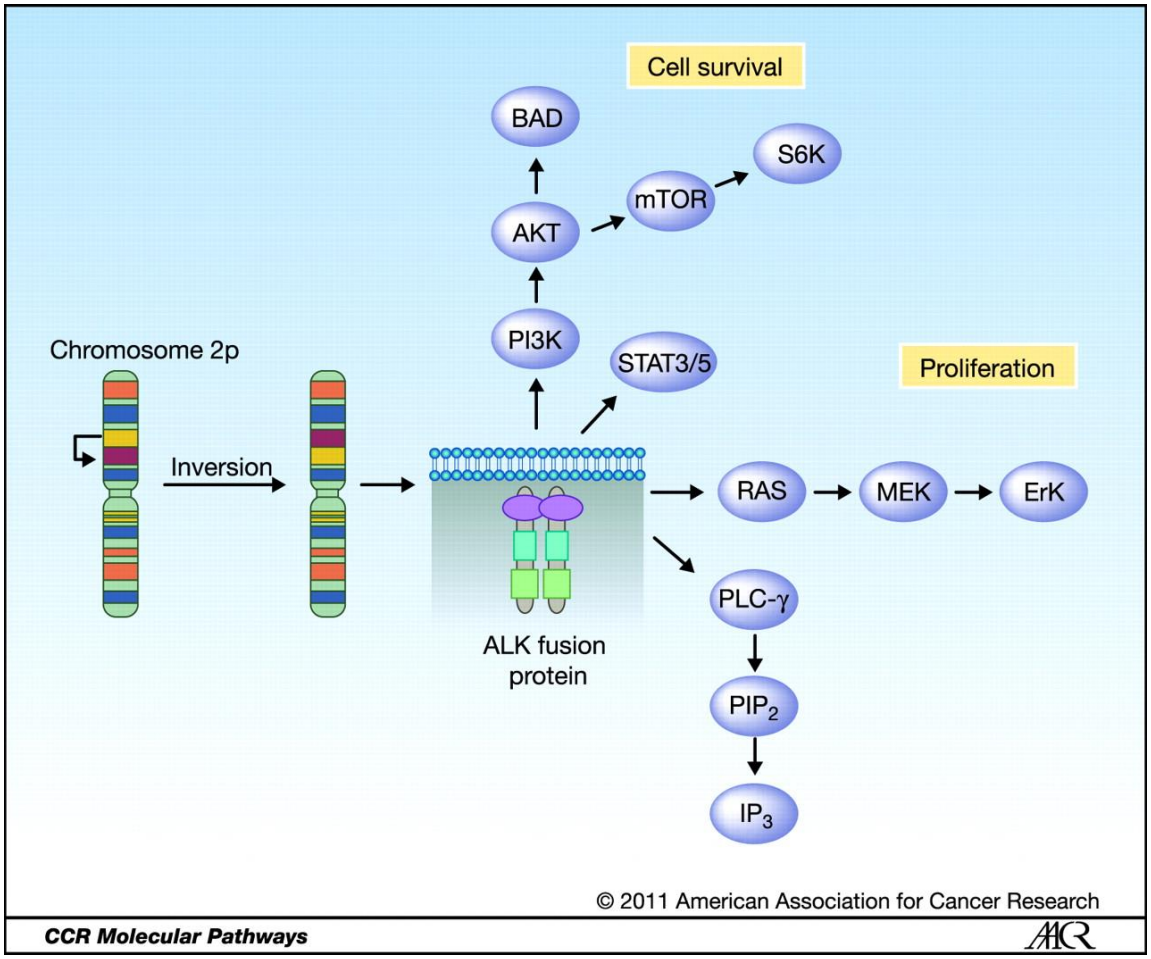
No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

	No. of Patients	Median Progression-free Survival *mo (95% CI)*
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

Mok et al. NEJM 2016

EML4-ALK fusion



Shaw AT, Solomon B. Clin Cancer Res. 2011

ALK fusion

- Occurs in 2 to 7% of all non–small-cell lung cancers
- Found almost exclusively in non-squamous NSCLC
- More prevalent in light or never smokers
- More prevalent in younger patients
- Prevalence does not appear to differ between Asian and Caucasian patients

TKIs: ALK fusion

- First generation
  - Crizotinib: oral small molecule TKI of ALK, MET and ROS1, HGFR
- Second Generation
  - Ceritinib: Targets ALK, ROS1, IGF-1R
  - Alectinib: Targets ALK and RET. More potent than crizotinib
  - Brigatinib: Multikinase inhibitor targeting ALK, ROS1, IGF-1R, FLT-3, EGFR
- Third Generation
  - Lorlatinib: Targets ALK, ROS1

ALK Fusion: First Line Therapy

- PROFILE 1014 (Solomon et al. NEJM 2014)
  - **Crizotinib** vs. platinum/pemetrexed in untreated advanced non-squamous ALK positive NSCLC
  - PFS 10.9 vs. 7 months, RR 74% vs. 45%
  - Median OS in both groups not reached
- ASCEND-4 (Soria et al. Lancet 2017)
  - **Ceritinib** vs. platinum/pemetrexed
  - PFS 16.6 vs. 8.1 months, RR 72.5% vs. 26.7%
  - No difference in OS but results immature
- ALEX (Peters et al. NEJM 2017)
  - **Alectinib** vs. **crizotinib**
  - PFS NR vs. 11.1 months, HR 0.47 RR 82.9% vs. 75.5% p=0.09
  - Significant decrease in CNS disease (12% vs. 45%)

TKIs: ALK fusion

- Resistance invariably occurs with majority progressing within 12 months
  - Secondary mutation in ALK tyrosine kinase domain
  - Amplification of ALK fusion gene
  - Bypass signaling pathways (EGFR, KIT, IGF1R)
- Second generation TKIs of ALK developed to overcome resistance

ALK Fusion: Second Line Therapy

- Yang et al. J Thorac Oncol. 2017
  - Pooled analysis of 2 phase 2 trials of **alectinib** in ALK positive patients with progression on crizotinib
  - ORR 51.3%, PFS 8.3 months, OS 26 months
- ASCEND-5 (Shaw et al. Lancet Oncol. 2017)
  - Phase 3 trial of **ceritinib** vs. chemotherapy in ALK positive patients with progression on crizotinib and platinum doublet
  - PFS 5.4 vs. 1.6 months, RR 45% vs. 8%
  - OS 18.1 months vs. 20.1 months (cross over allowed)

ROS1

- Driver mutation found in 1-2% of advanced non-squamous lung cancers
- Chromosomal rearrangement leads to fusion of a portion of ROS1 that includes the entire tyrosine kinase domain with 1 of 12 different partner proteins.
  - The resulting ROS1 fusion kinases are constitutively activated and drive cellular transformation
- Inhibited by both crizotinib and ceritinib

ROS1

- Lim et al. J Clin Oncol 2017
  - Phase II trial of **ceritinib** in patients with ROS1 mutation in patients who had progressed on standard therapy
  - RR 62%, PFS 9.3 months for all pts (19.3 for crizotinib naïve pts)
  - Median OS 24 months

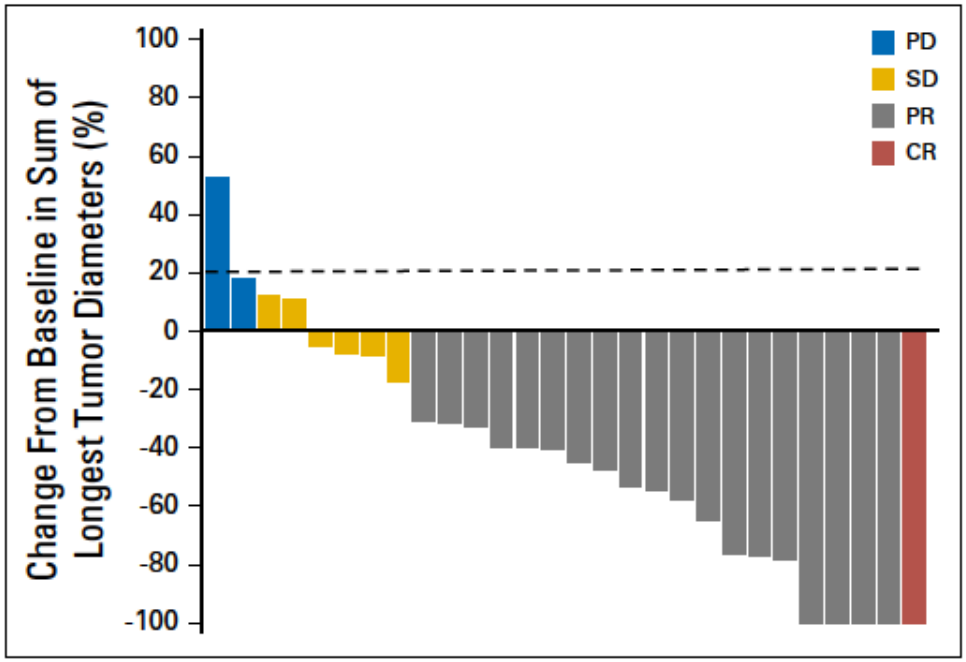


Fig 1. Best percentage change from baseline in tumor volume in patients with at least one postbaseline measurement. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Which patients should be tested?

- ASCO Guideline:
  - "Use testing for EGFR mutations and ALK rearrangements to guide patient selection for therapy with EGFR or ALK inhibitors, respectively, in **all patients** with **advanced-stage lung adenocarcinoma or tumors with an adenocarcinoma component**, irrespective of clinical characteristics (eg, smoking history, sex, race, or other clinical factors)."
  - Primary and metastatic tumors suitable for testing

Leighl et al. J Clin Oncol. 2014

Toxicities associated with EFGR TKIs

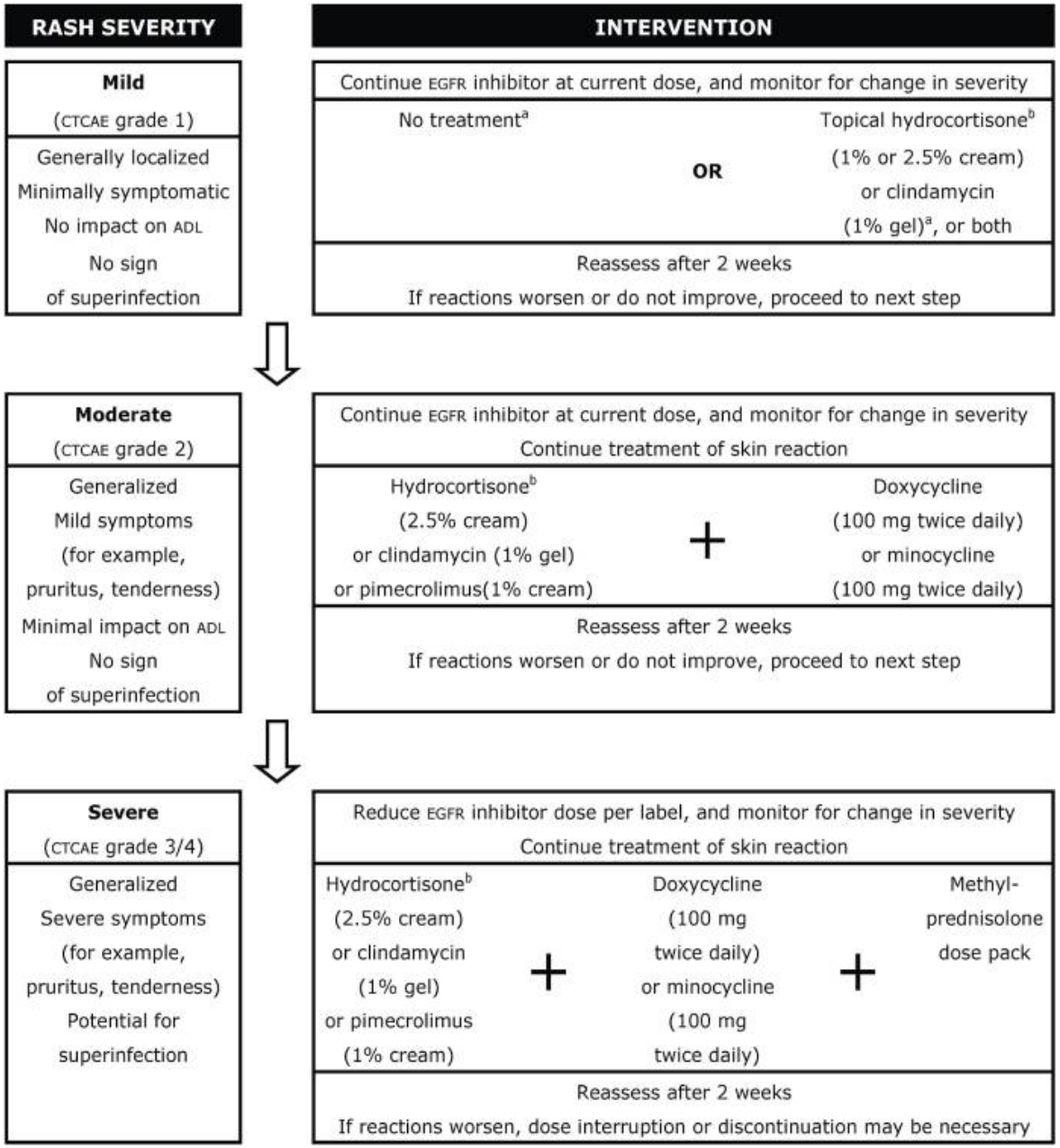
- Rash
  - Occurs in ~65% of patients. Most common adverse event.
  - Follicular acneiform eruption
  - Pruritus, hair changes and alopecia, nail alterations, and hand and foot reactions
  - More common with afatinib
  - Correlates with response to therapy
- Diarrhea
  - Occurs in ~55% of patients. Second most common adverse event
  - Secretory form – excess chloride secretion
  - Also more common with afatinib

Hirsch V et al. Curr Oncol. 2014

Toxicities associated with EGFR TKIs

- Pneumonitis
  - Rare, <1% - 5%, but most common cause of treatment related deaths
  - Can be difficult to distinguish between infection, progression of malignancy
  - Diagnosis requires higher index of suspicion, imaging
  - Treatment involves discontinuing TKI, glucocorticoids +/- empiric antibiotics and supportive measures (admission, O2 etc.)
- Hepatotoxicity
  - Elevated LEs occur in 20-60%, more common with gefitinib
  - Grade 3 or greater in 2-10%
  - Discontinue TKI, restart with dose reduction or consider rotating to alternate TKI

Approach to TKI Rash



Hirsch V et al. Curr Oncol 2011

Approach to TKI diarrhea

Grade	Intervention
1 - Mild	• Stop laxatives. Drink 8–10 glasses of clear fluids daily. • Immediately start loperamide: 4 mg (2 tablets) followed by 2 mg (1 tablet) after each loose stool (up to 20 mg daily) until bowel movements cease for 12 hours. • Maintain dose level of EGFR TKI.
2 - Moderate	• See grade 1. • Continue loperamide. Assess for dehydration and electrolyte imbalance. Consider intravenous • fluids and electrolyte replacement. • If diarrhea does not improve after 48 hours, temporarily discontinue EGFR TKI. Upon improvement to grade 1 restart EGFR TKI at a reduced dose (except gefitinib, which should be restarted at the original dose).
3/4 – Severe/Life threatening	• See grade 2 • Plus: Use stool cultures to rule out an infectious process. Apply aggressive intravenous fluid replacement for 24 hours or more. • Use hospitalization to monitor the patient's progress. Consider prophylactic antibiotics if the patient is also neutropenic. • Temporarily discontinue EGFR TKI. Upon improvement to grade 1, restart EGFR TKI at a reduced dose (except gefitinib, which should be restarted at the original dose). • Permanently discontinue EGFR TKI if diarrhea does not return to grade 1 within 14 days despite treatment discontinuation and best supportive care.

Hirsch V et al. Curr Oncol 2014

Toxicities associated with ALK/ROS1 TKIs

Table 3. Safety Overview and Adverse Events of Any Grade That Differed by 5 Percentage Points or More in Frequency between Groups.*

Event	Crizotinib (N=151)		Alectinib (N=152)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5
	number of patients (percent)			
Adverse event	146 (97)	76 (50)	147 (97)	63 (41)
Serious adverse event	—	44 (29)	—	43 (28)
Fatal adverse event†	—	7 (5)	—	5 (3)
Nausea	72 (48)	5 (3)	21 (14)	1 (1)
Diarrhea	68 (45)	3 (2)	18 (12)	0
Vomiting	58 (38)	5 (3)	11 (7)	0
ALT increased	45 (30)	22 (15)	23 (15)	7 (5)
AST increased	37 (25)	16 (11)	21 (14)	8 (5)
Blood bilirubin increased	2 (1)	0	23 (15)	3 (2)
Weight increased	0	0	15 (10)	1 (1)
γ-Glutamyltransferase increased	10 (7)	2 (1)	1 (1)	1 (1)
Peripheral edema	42 (28)	1 (1)	26 (17)	0
Dizziness	21 (14)	0	12 (8)	0
Dysgeusia	29 (19)	0	4 (3)	0
Visual impairment	18 (12)	0	2 (1)	0
Vision blurred	11 (7)	0	3 (2)	0
Photopsia	9 (6)	0	0	0

Peters et al. NEJM 2017

Summary

- Targetable mutations exist in a proportion of non-squamous non-small cell lung cancers
  - EGFR – 15%
  - ALK – 5%
  - ROS1 - 1-2%
- In patients with stage IV disease, first line treatment with a TKI is standard of care
  - In patients with EGFR mutations with progression on first line TKI, rebiopsy (or ctDNA) for T790M mutation
- All patients with advanced non-squamous NSCLC should undergo testing for a driver mutation
- TKIs have a unique spectrum of toxicity requiring specific monitoring and interventions

Questions