Lung Cancer in 2014: The New Paradigm

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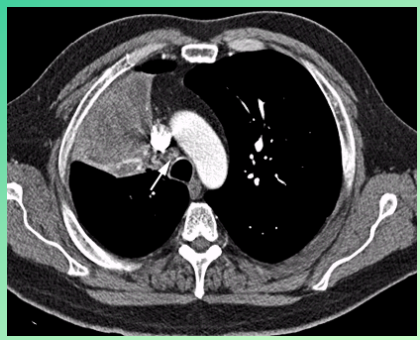
Case Presentation

- 62 year old man, former smoker, presented to his PCP with a cough that would not go away
- Treated briefly symptomatically without benefit
- Chest X-ray then obtained that showed lung mass and suggestion of mediastinal fullness
- CT scan obtained…

CT Scan showing lung mass and paratracheal adenopathy



Case, continued

- Staged as Stage IIIA with ipsilateral mediastinal lymph node involvement
- Started on radiation and chemotherapy with weekly Paclitaxel and Carboplatin in hopes of rendering him a surgical candidate
- Response to therapy insufficient to justify exploratory thoracotomy
- After this treatment was finished he was observed until further progression

Case, continued

- Nine months later there was evidence of progressive disease in the lung and mediastinum
- Chemo was restarted, this time Gemcitabine and Cisplatin
- No response to therapy
- His cough and dyspnea worsened and he began losing weight

Case, continued

- At this point, running out of options, I retrieved the paraffin block of his tumor and sent a specimen for the presence of a mutation in the Epidermal Growth Factor Receptor to a commercial lab
- The test came back showing a mutation and he was started on Erlotinib (Tarceva®)
- For the next two years his tumor gradually shrank and his sense of well being improved
- He is still in partial remission three years after starting Erlotinib
- Toxicity has been manageable, mostly skin rashes requiring intermittent stopping of the drug, without tumor regrowth

"Greed is Good"

Gordon Gekko, 1987

- The race to sequence the human genome between the NIH and Craig Venter resulted in an explosion of knowledge
- Venter and Francis Collins, Director of NIH, jointly announced success in 2000 years ahead of schedule; Venter was the catalyst for the rapid advances
- The economic fallout from this project has been staggering

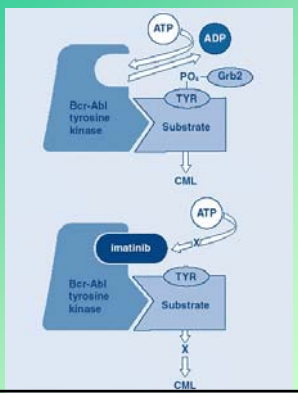
The Human Genome Project and Cancer Research

- An early observation of the genome project is that there are variations from normal that are bad for your health
- Some mutations are inherited – e.g. the BRCA and von Hippel Lindau gene mutations – and convey a lifetime risk of getting cancer
- Other mutations are organ and tumor specific – so-called somatic rather than germ-line mutations – present only in the tumor, not in the rest of the cells of the individual
- Examples…

The BCR-ABL translocation in Chronic Myelogenous Leukemia

- Recall that the translocation of genetic material between chromosomes 9 and 22 in bone-marrow stem cells results in a novel gene (BcrAbl) and a novel tyrosine kinase that gives the cell so affected a growth advantage
- Imatinib (Gleevec®) was invented to block this novel gene by interfering with its function by inserting a poisonous drug into a crucial slot in this novel tyrosine kinase

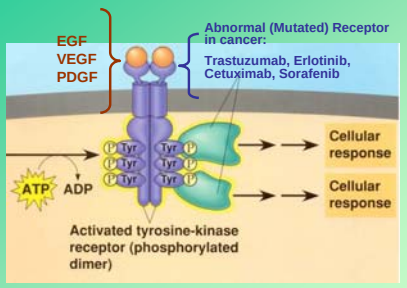
How Imatinib Works



Can this concept, so effective in CML, be exported to other diseases?

- Mutations in receptors on the surface of normal and cancer cells have been uncovered and offer new targets for therapy
- The Her-2 gene, over-expressed in a minority of breast cancers, and conveying a growth advantage to the cancer cell, can be blocked by Trastuzumab, or Herceptin®

Other Tyrosine Kinase inhibitors



All these drugs ultimately work to modulate the phosphorylation of tyrosine

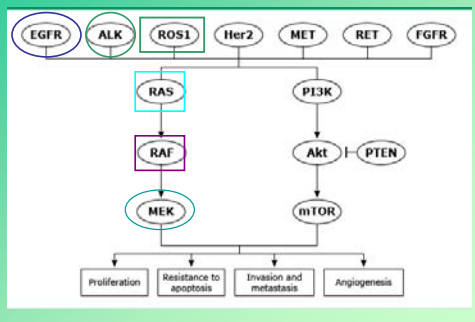
Mutations: Drivers and Passengers

- What are Driver Mutations?
  - Some somatic mutations in cancer cells have been identified whose role is murky; they do not seem critical to the survival and proliferation of the cell; these are called passenger mutations
  - Driver mutations have several critical features…

Driver Mutations

- Convey a critical growth advantage and enhanced metastatic potential to the cancer cell
- The cell becomes "addicted" to these gene products – i.e., the cell soon cannot survive without the protein products of that gene
- Blocking that gene product pharmacologically can then result in cell death

Driver Mutations/Molecular Targets in NSCLC



Testing for Driver Mutations

- Comprehensive sequencing ("whole exome"); expensive and time consuming and false negative with current technology if the mutation is not expressed in most of the cells tested
- Next generation sequencing: relies on computerized automation and massively parallel approach; not yet in routine commercial use

Testing, continued

- PCR testing; relies on knowing what you are looking for; very useful for routine clinical testing of specimens rather than research to uncover new mutations
- FISH testing: long history, highly automated, exportable to the clinical lab; again you have to know in advance what you are looking for

The New Testing Paradigm

- Multiplex Genotype Testing
- Allows parallel simultaneous testing for several mutations rather than sequencing testing – e.g., if EGFR is negative, try the next test
- Proof of principle recently presented in a landmark paper published in May, 2104 in JAMA…we will talk about this later

EGFR Mutations and Tyrosine Kinase Inhibitors

- Two drugs have been developed to full clinical use to block the Epidermal Growth Factor Receptor: Gefitinib and Erlotinib
- Gefitinib was tested over ten years ago before EGFR testing was widespread and the results in the unselected population of patients with NSCLC were disappointing, so the drug was shelved in the US

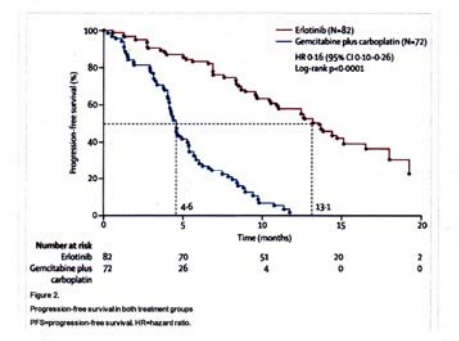
EGFR and Erlotinib

- Newer drug; clinical trials benefitted from patient selection (only 20% of patients with adenocarcinoma have EGFR-mutated tumors)
- Key trial conducted in Asia showed the extent to which the selection of patient and mutation could influence outcome…

The EGFR in NSCLC

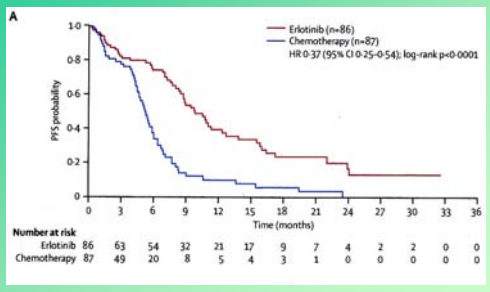
- Seen predominantly in Asian non-smoking women
- Study from several institutions in the Far East looked at this:
  - 1482 patients with newly diagnosed Stages IIIB/IV adenocarcinoma of the lung
  - 43% women
  - 61% of tumors in women contained the key mutation
  - 44% of men
  - Highest rate in never smokers
  - Much higher frequency than seen in Caucasian patients in the US (recall: about 20%)

Results of OPTIMAL Trial: Erlotinib vs. Chemo
In EGFR mutated non-small-cell lung cancer (mostly adenoca)

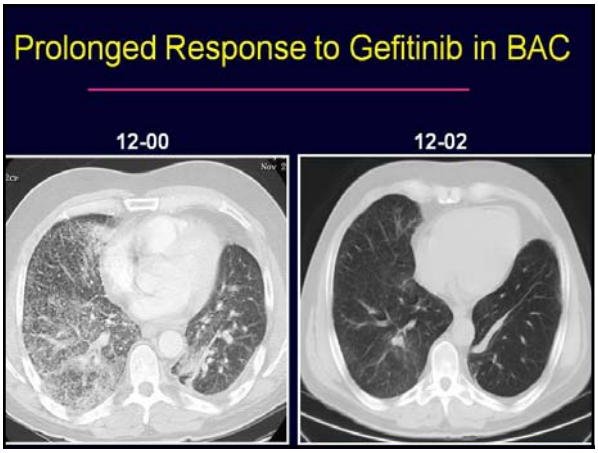


Zhou et al *The Lancet Oncology* 12:735, 2011

Erlotinib vs. Chemo in European Patients
With EGFR Mutation



Rosell et al. *The Lancet Oncology* 13:239, 2012



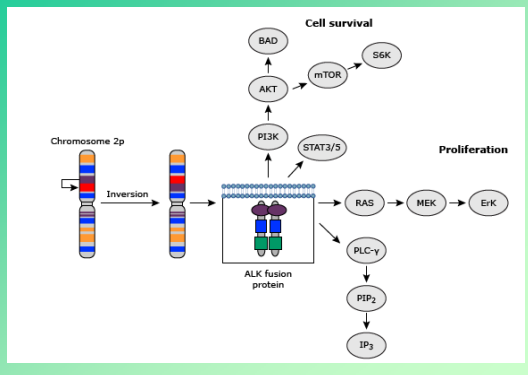
Toxicities of EGFR Antagonists

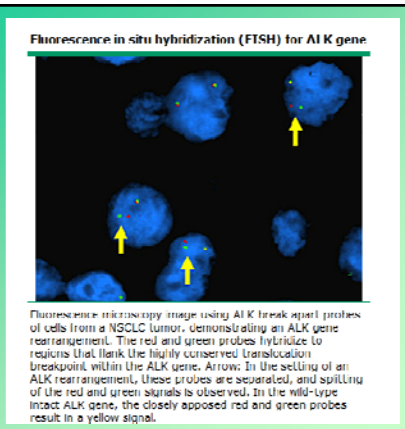
- Free from most of the usual chemotherapy toxicities
- Caused usually by TK inhibition in normal tissue
- Skin rash and diarrhea are dose dependent and reversible; often result in delays in treatment and dose attenuation
- Conjunctivitis common and annoying
- Pulmonary toxicity is rare but can be serious; if present drug must be discontinued, not dose reduced
- Dose response anti-tumor relationship for these drugs not clear yet, but usually more is better

The ALK Fusion Oncogene

- ALK, or anaplastic lymphoma kinase, gene rearrangement is the name given a new DNA sequence resulting from a translocation of a small amount of genetic material on chromosome 2 in about 5% of adenocarcinomas of the lung

The ALK rearrangement, shown schematically





Fluorescence microscopy image using ALK break apart probes of cells from a NSCLC tumor, demonstrating an ALK gene rearrangement. The red and green probes hybridize to regions that flank the highly conserved translocation breakpoint within the ALK gene. Arrow: In the setting of an ALK rearrangement, these probes are separated, and splitting of the red and green signals is observed. In the wild-type intact ALK gene, the closely apposed red and green probes result in a yellow signal.

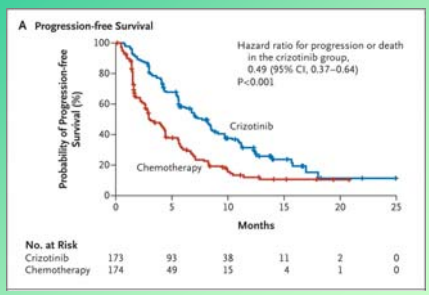
ALK – Clinical Characteristics

- Same group who harbor the EGFR mutation:
  - Never smokers
  - Asians
  - Women
- If such patients are EGFR mutation negative they have a 1/3 chance of being Alk positive – vs. 5% of all lung cancer patients

ALK Positivity: Implications

- Crizotinib is a TKI recently developed that in early clinical testing showed remarkable activity against ALK+ adenocarcinoma of the lung
- Ceritinib is 20 X more potent and has just been approved for Crizotinib failures
- The Crizotinib data…

Progression-free Survival in Alk-Positive Patients Who Have Already Progressed on Platinum-Based Chemotherapy



Shaw AT et al. *N Engl J Med* 2013;368:2385-2394.

The ROS-1 Translocation

- Tyrosine kinase receptor of the insulin receptor family
- Driver oncogene in 1-2% of NSCLC
- Patients who harbor this gene fit the same demographic as the EGFR+ and Alk+ patients
- Preliminary data show tumors from such patients are highly sensitive to Crizotinib

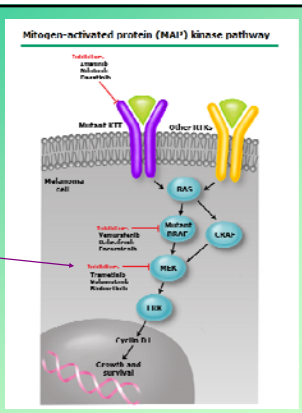
Unique Toxicities of Crizotinib

- Rapid and dramatic reduction of serum testosterone; clinically significant, requires testosterone replacement
- Peripheral neuropathy more common than with other TKI's
- Cardiac toxicity: Sinus bradycardia and QTc prolongation, requiring frequent cardiac clinical and electrical evaluations

KRAS Mutations

- One of the most common driver mutations seen in oncology
- Originally described in pancreatic cancer, initially seemed to be influenced by statins
- Seen in a wide variety of cancers
- Thus far no drugs have been found that work directly on lung cancer KRAS mutants; however….

MEK inhibition in KRAS mutant tumors seems to be beneficial



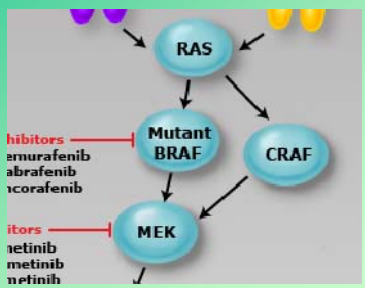
KRAS/MEK inhibition, continued

- MEK inhibitors alone showed no clinical benefit despite promise *in vitro*
- Adding erlotinib to MEK inhibitors did nothing
- Farnesyl transferase inhibitors – at one time leading candidates for mutant KRAS anti-tumor therapy – are inactive in lung cancer
- Preclinical data suggested synergy between MEK inhibitor Selumetinib and Docetaxel

Selumetinib

- Still in clinical trials; not commercially available
- MEK inhibitor
- Has shown benefit in patients with well differentiated thyroid cancer and metastatic melanoma
- Many thyroid cancers contain BRAF and KRAS mutations, which occur upstream from MEK, so interfering with MEK would sabotage tumor stimulating effects of these mutations

The Downstream Position of MEK



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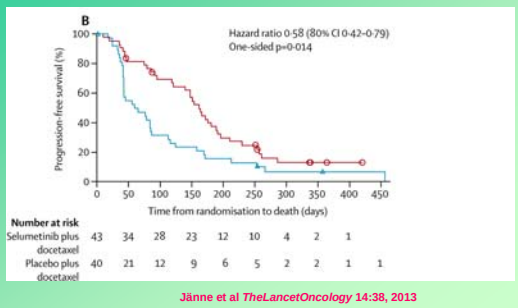
- Increases RAI uptake in patients whose thyroid cancer had become iodine independent (*NEJM* 368:623, 2013)

Impact of adding Selumetinib to Docetaxel in Patients with KRAS-Mutant Stages IIIB-IV NSCLC in Relapse from Prior Therapy



Jänne et al *TheLancetOncology* 14:38, 2013

BRAF inhibition

- Found very useful in selected melanoma patients whose tumor harbor a specific BRAF mutation; inadequately tested in lung cancer but in theory might be another downstream way to deal with KRAS mutations
- Unique toxicity: cutaneous squamous cell carcinoma develops in up to 30% of patients given BRAF inhibitors; can happen within weeks of starting therapy; if numerous can require discontinuation of therapy

Additional Driver Mutations

- There have been identified a number of other driver mutations, all subjects of active clinical investigation
- Nothing to report yet of clinical significance to patients with NSCLC

Putting All of This Information Together

- Blockbuster landmark study published in JAMA in May 2014 looking at a number of these issues
- Took archival tumor tissue from over 1000 patients at MSKCC, DFCI and elsewhere and performed Multiplex assays of driver mutations (simultaneous probing of up to ten drivers)

Kris et al *JAMA* 311:1998, 2014

JAMA study, continued

- Oncogenic driver mutation found in 64% of tumors tested
  - 25% KRAS
  - 17% EGFR
  - 8% Alk
  - Her-2 3%
  - BRAF 2%
  - All the rest other more obscure mutations
  - 3% of the tumors had more than one mutation – previously thought not to happen

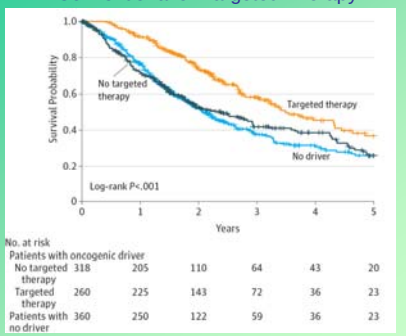
Complete Results of Multiplex Assay of Potential Driver Mutations

Gene With Mutational or Structural Change	Genotyping, No. (%) [95% CI]		Patients Receiving Targeted Therapy, No. (%)[c]
	Any (n = 1007)[a,b]	Full (n = 733)[b]	
Any gene(s)	623 (62) [59-65]	466 (64) [60-67]	275 (44)
Singletons[d]			
KRAS	245 (24) [22-27]	182 (25) [22-28]	22 (9)
EGFR (sensitizing)[e]	175 (17) [15-20]	122 (17) [14-20]	146 (83)
exon19 del	103 (10) [9-12]	68 (9) [7-12]	
L858R	64 (6) [5-8]	47 (6) [5-9]	
G719X	5 (0.5) [0.2-1]	5 (0.7) [0.3-2]	
L861Q	5 (0.5) [0.2-1]	4 (0.5) [0.2-2]	
ALK (rearrangement)	80 (8) [6-10]	57 (8) [6-10]	52 (65)
EGFR (other)[f]	35 (4) [3-5]	29 (4) [3-6]	23 (66)
ERBB2 (formerly *HER2*)	23 (2) [2-4]	19 (3) [2-4]	11 (48)
BRAF	18 (2) [1-3]	16 (2) [1.3-3.6]	3 (17)
V600E	14 (1) [0.8-2]	12 (2) [0.9-3]	2 (14)
Non-*V600E*	4 (0.4) [0.1-1]	4 (0.5) [0.2-2]	1 (25)
PIK3CA	7 (0.7) [0.3-2]	6 (0.8) [0.3-2]	0
MET (amplification)	6 (0.6) [0.2-1]	5 (0.7) [0.3-2]	3 (50)
NRAS	5 (0.5) [0.2-1]	5 (0.7) [0.3-2]	0
MEK1	2 (0.2) [0.03-1]	1 (0.1) [0-1]	0
AKT1	0 [0-1]	0 [0-1]	0
Doubletons			
>1 gene	27 (3) [2-4]	24 (3) [2-5]	15 (56)

JAMA, continued

- Non-randomized trial, therapy up to the discretion of the clinician
- Retrospective analysis of outcome with the major variable examined whether the patient received targeted therapy or conventional chemotherapy
- Major limitation of study was the presence of FDA approved drugs for only two targets (EGFR and Alk), so some patients with driver targets received off-label drugs (e.g., Trastuzumab) or investigational drugs, for which no efficacy data are available yet, potentially diluting a positive outcome

Patients with Stages IIIB/IV NSCLC Treated with Conventional or Targeted Therapy



Kris et al *JAMA* 311:1998, 2014

Where is All of This Going?

- If you go to MSKCC or Dana Farber with advanced lung cancer today they will do complete driver mutation analysis before giving you any therapy
- Highly likely that mutation analysis technology will filter down to become available soon to community oncology practices through commercial reference labs
- As new mutations are discovered and new drugs developed a smaller and smaller minority of lung cancer patients (and cancer patients in general) will receive conventional chemotherapy in the future

Conclusions

- DNA sequencing technology has allowed investigators to identify mutations in cancers that drive them to become malignant
- Those mutations produce novel proteins that convey a growth advantage to those cells
- Drugs designed to block the protein products of the mutations have revolutionized the treatment of advanced lung cancer; unusual side effects will be uncovered

- [I have no financial relationships to any of the companies making any of the drugs or diagnostic tests discussed.]