Non-Small Cell Lung Cancer (NSCLC) Therapeutics: State of the Art

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Disclosures

• Research Grants: BMS/ImClone, Genentech, Lilly, Merck, Novartis, Sanofi-Aventis

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Therapeutic Advances in the Last 5-10 Years

**NSCLC** (Advanced Stage)
- Biomarker-driven therapy for *EGFR*-mutant *ALK*-positive NSCLC and targeted therapy (*EGFR* TKIs & Crizotinib)

**NSCLC** (Early Stage)
- No major advances

**SCLC** (Limited & Extensive)
- No major advances

**Unmet Needs to Advance Personalized Therapy in NSCLC**
- Recognition of lung cancer complexity at the genomic level -including inter- and intra patient tumor heterogeneity
- Integration of this genomic complexity into clinical decision-making process
- Integration of this genomic complexity into biomarker-driven drug development & clinical trial designs
**Adjuvant Chemotherapy for NSCLC**  
**LACE Analysis by Stage**

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Deaths / No. Entered</th>
<th>Hazard (Chemotherapy / Control)</th>
<th>HR</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA</td>
<td>104 / 347</td>
<td>[Chemotherapy better]</td>
<td><strong>1.41</strong></td>
<td>[0.96;2.09]</td>
</tr>
<tr>
<td>Stage IB</td>
<td>515 / 1371</td>
<td></td>
<td>0.92</td>
<td>[0.78;1.10]</td>
</tr>
<tr>
<td>Stage II</td>
<td>893 / 1616</td>
<td></td>
<td>0.83</td>
<td>[0.73;0.95]</td>
</tr>
<tr>
<td>Stage III</td>
<td>878 / 1247</td>
<td></td>
<td>0.83</td>
<td>[0.73;0.95]</td>
</tr>
</tbody>
</table>

Test for trend:  \( P = 0.051 \)

Adjuvant chemotherapy has greatest benefit for stage II and III and may be detrimental for stage IA

Impact of Adjuvant Chemotherapy in Operable NSCLC: Two meta-analyses of individual patient data

34 trials, 8447 patients
HR 0.86 (95 CI: 0.81-0.92)
P<0.0001

13 trials, 2660 patients
HR 0.88 (95 CI: 0.81-0.97)
P<0.009

4% absolute benefit

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>S alone</th>
<th>S+CT</th>
<th>S+RT</th>
<th>S+CT+RT</th>
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<tbody>
<tr>
<td>0</td>
<td>4142</td>
<td>4305</td>
<td>1345</td>
<td>1315</td>
</tr>
<tr>
<td>1</td>
<td>3648</td>
<td>3809</td>
<td>956</td>
<td>977</td>
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<tr>
<td>2</td>
<td>3102</td>
<td>3261</td>
<td>660</td>
<td>711</td>
</tr>
<tr>
<td>3</td>
<td>2584</td>
<td>2746</td>
<td>503</td>
<td>532</td>
</tr>
<tr>
<td>4</td>
<td>2083</td>
<td>2278</td>
<td>376</td>
<td>385</td>
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<td>5</td>
<td>1601</td>
<td>1785</td>
<td>282</td>
<td>279</td>
</tr>
<tr>
<td>6</td>
<td>841</td>
<td>936</td>
<td>202</td>
<td>203</td>
</tr>
<tr>
<td>7</td>
<td>407</td>
<td>473</td>
<td>141</td>
<td>143</td>
</tr>
<tr>
<td>8</td>
<td>148</td>
<td>165</td>
<td>85</td>
<td>84</td>
</tr>
</tbody>
</table>

NSCLC Meta-analyses Collaborative Group Lancet 2010; 375:1267
Potential Benefit from Adjuvant Chemotherapy

100% of “unselected patients” receiving Adjuvant Chemotherapy

What proportion benefit?
What proportion are already cured with Surgery alone?
What proportion have resistant cancers & could be spared Chemotherapy?

“Unselected=not selected by a predictive biomarker
Potential Benefit from Adjuvant Systemic Therapy

All Patients treated with Adjuvant Chemotherapy

- Patients with residual micrometastases resistant to adjuvant therapy
  - Predictive Biomarkers?

- Patients already cured with Surgery alone
  - Prognostic Biomarkers?

Patients with micrometastases sensitive to adjuvant therapy (unselected)
Pervenio™ Lung RS Prospective Trial: Does this prognostic gene signature have predictive value in High Risk Stage I Patients?

**Pervenio™ Lung RS Prognostic Analysis**

- High Risk
  - Randomization
  - Excluded
  - Observation

- Intermediate Risk
  - Excluded
  - Observation

- Low Risk
  - Observation

**Molecular Prognostic analysis:**
- R0 resection
- Non-squamous NSCLC
- Pathologic stage I

**Chemotherapy**
- 4 cycles cisplatin doublet
- Routine CT scans
- DFS
- OS

**Observation**
- Routine CT scans
- DFS
- OS
ALCHEMIST
(Do predictive biomarkers in advanced stage translate into early stage adjuvant therapy?
-Next Generation Sequencing on 6-8,000 post-surgical NSCLC cases

Stage IB- IIIA NSCLC
Complete Surgical Resection

Erlotinib X 2 years
Placebo

Screen for EGFR mutation+ cancers
Adjuvant Therapy (if indicated)

Crizotinib X 2 years
Placebo

Screen for ALK+ cancers
Adjuvant Therapy (if indicated)

Stage IB- IIIA NSCLC
Complete Surgical Resection

A081105

E4517
Updated Treatment Algorithm for Advanced-Stage NSCLC (2013)

Proposed Treatment Algorithm

- EGFR Mutation Positive or ALK Positive
  - Molecular
    - Good PS
      - Clinical (PS)
    - Poor PS
      - Clinical (PS)
  - Non-squamous
    - Histologic
      - Squamous
      - Single-Agent Or Combination Chemotherapy
    - Clinical
      - Bevacizumab Eligible
        - Platinum/Pemetrexed (or Other*) ± Bevacizumab
      - Bevacizumab Ineligible
        - Platinum/Pemetrexed (or Other*)
      - Platinum Doublet*

End of First-line Chemotherapy

- Progression
  - Bevacizumab, Erlotinib, Pemetrexed Or Observation
  - Erlotinib or Pemetrexed Or Observation
  - Erlotinib Or Observation

Based on Prior Therapy

*with docetaxel, paclitaxel, gemcitabine, vinorelbine

from Gandara, Mack, Li, Lara, Herbst: Clin Lung Cancer, 2009
Transition from Empiric to Personalized Cancer Therapy (Molecular-Based)

Empiric Therapy

Molecular-Based & Personalized Therapy

Patient Characteristics
Available Literature
Physician Experience

Tumor Molecular Profiling to identify drug targets (adequate tissue)

Drugs against the Molecular Targets

Predictive Biomarkers for the drugs

Multi-drug therapy

Evolution of NSCLC Subtyping from Histologic to Molecular-Based

Li, Gandara et al: JCO 2013 (adapted from Pao et al)
EGFR Mutations
About 12% of NSCLC
In USA (40% in Asia)

Most common in:
- Adenocarcinoma (~BAC)
- Never-Smokers
- East Asians
- Females
- Younger patients

But cannot rule in or rule out EGFR mutation based on characteristics

Lynch: NEJM 2004
IPASS: EGFR TKI versus Chemotherapy:
Progression-free survival in EGFR mutation positive & negative cancers

**EGFR mutation positive**

EGFR TKI (n=132)
Chemotherapy (n=129)

HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001

**EGFR mutation negative**

EGFR TKI (n=91)
Chemotherapy (n=85)

HR (95% CI) = 2.85 (2.05, 3.98)
p<0.0001

EGFR Mutation status dictates patient outcomes from therapy independent of clinical characteristics

*Mok: NEJM, 2009*
## First-line Treatment With EGFR TKIs vs Chemotherapy in EGFR-Mutated NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>Median PFS (mos)</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maemondo[1]</td>
<td>Gefitinib vs carboplatin/paclitaxel</td>
<td>230</td>
<td>10.8 vs 5.4 ($P &lt; .001$)</td>
<td>30.5 vs 23.6 ($P = .31$)</td>
</tr>
<tr>
<td>Mitsudomi[2,3]</td>
<td>Gefitinib vs cisplatin/docetaxel</td>
<td>177</td>
<td>9.2 vs 6.3 ($P &lt; .0001$)</td>
<td>36 vs 39 (HR: 1.19)</td>
</tr>
<tr>
<td>OPTIMAL[4,5]</td>
<td>Erlotinib vs carboplatin/gemcitabine</td>
<td>165</td>
<td>13.1 vs 4.6 ($P &lt; .0001$)</td>
<td>HR: 1.065 ($P = .65$)</td>
</tr>
<tr>
<td>EURTAC[6]</td>
<td>Erlotinib vs platinum-based chemotherapy</td>
<td>174</td>
<td>9.7 vs 5.2 ($P &lt; .0001$)</td>
<td>19.3 vs 19.5 ($P = .87$)</td>
</tr>
<tr>
<td>LUX-Lung 3[7]</td>
<td>Afatanib vs CDDP/pemetrexed</td>
<td>345</td>
<td>11.1 vs 6.9 ($P &lt; .0004$)</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

ALK Fusion in NSCLC

ALK Rearrangement in NSCLC

- Present in ~4% of NSCLC cases
- Enriched in younger never or light smokers with adenocarcinoma (~20%)
- Rarely overlaps with EGFR or KRAS mutations (de novo)

Clinical Testing

- IHC
- RT-PCR
- Break apart FISH Assay

- ALK-specific inhibitor Crizotinib: ~60% RR

Camidge et al: ASCO 2011; Abs #2501
Incorporation of Molecular Profiling into Therapeutic Decision-Making Process for Advanced NSCLC

Summary Guidelines for 2013

- **Who to test?:** Patients with NSCLC and adenocarcinoma component
- **What to test for?:** *EGFR* mutation and *ALK* fusion (+ others?)
- **What specimen?:** core needle biopsy (or multi-pass FNA), cytology cell block, surgical biopsy (bone biopsy problematic)
- **How to test?:** concurrently (not sequentially test-by-test)
- **How long a turn-around time is acceptable?:** <2 weeks
- **When to test?:** at the time of diagnosis (not just when treatment decision needed)
- **When to re-test?:** after PD from a targeted therapy intervention (to assess for tumor evolution in the molecular profile)

Magnitude of Genomic Derangement is greatest in Lung Cancer

Lung Cancer Complexity on an Individual Patient Basis (“Circos”)

from Ramaswamy Govindan
TCGA (The Cancer Genome Atlas)
Genotyping & Genomic Profiling in Personalized Medicine: Evolution in Therapeutic Application over time

1. Histomorphological Diagnosis:

2. Molecular Diagnosis:
   - Archival FFPE tumor specimens

Current Approach (Target-Based Therapy V1.0):
   - Use single gene molecular testing for decision-making in an individual patient

Evolving Approach (Target-Based Therapy V2.0):
   - Use multiplexed molecular tests with increased sensitivity & output for decision-making in an individual patient

Near-Future Approach (Patient-Based Therapy):
   - Use genomic profiling from high throughput next generation sequencing for decision-making in an individual patient

Empiric Approach (Compound-Based Therapy):
   - Use clinical-histologic factors to select drugs for an individual patient

Archival cancer specimens

Macro- or Micro-dissection of Tumors

Extract tumor nucleic acids:

DNA and RNA

Representative technologies:

- Single Biomarker Tests:
  - Sanger DNA Sequencing
  - RT-PCR
  - FISH
  - IHC

- Multiplex, Hot Spot Mutation Tests:
  - PCR-based SNapShot
  - PCR-based Mass Array SNP
  - Sequenom

- Initial High-Throughput Technologies:
  - SNP/CNV DNA microarray
  - RNA microarray

- Next Generation Sequencing (NGS):
  - Whole Genome or Exome capture Sequencing (DNA)
  - Whole or Targeted Transcriptome Sequencing (RNA)
  - Epigenetic profiling

from Li, Gandara et al: JCO, 2013
Therapeutic Advances in the Last 5-10 Years

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  - including inter- and intra patient tumor heterogeneity
- Integration of this genomic complexity into clinical decision-making process
- Integration of this genomic complexity into biomarker-driven drug development & clinical trial designs
### Classic RCT Design (Unselected): Phase III Trials of Chemotherapy +/- Targeted Agent* in 1<sup>st</sup>-line Therapy of Advanced Stage NSCLC

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>Survival Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMPs</td>
<td>Prinomastat, Others</td>
<td>No</td>
</tr>
<tr>
<td>EGFR TKI</td>
<td>Gefitinib or Erlotinib</td>
<td>No</td>
</tr>
<tr>
<td>Farnesyl Transferase (RAS)</td>
<td>Lonafarnib</td>
<td>No</td>
</tr>
<tr>
<td>PKCα</td>
<td>ISIS 3521</td>
<td>No</td>
</tr>
<tr>
<td>RXR</td>
<td>Bexarotene</td>
<td>No</td>
</tr>
<tr>
<td>VEGFR (TKI)</td>
<td>Sorafenib</td>
<td>No</td>
</tr>
<tr>
<td>VEGF (Mab)</td>
<td>Bevacizumab</td>
<td>Yes</td>
</tr>
<tr>
<td>EGFR (Mab)</td>
<td>Panitumumab</td>
<td>No</td>
</tr>
<tr>
<td>TLR9 Agonist</td>
<td>PF-351</td>
<td>No</td>
</tr>
<tr>
<td>EGFR (Mab)</td>
<td>Cetuximab</td>
<td>Yes**</td>
</tr>
<tr>
<td>IGR1-R</td>
<td>Figitumumab</td>
<td>No</td>
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<tr>
<td>VDA</td>
<td>ASA-404</td>
<td>No</td>
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</table>

Need for a completely “New Way of Thinking” for development of Targeted Drug/Biomarker Combinations: “Master Protocol”
Parallel Efforts in “Master Protocol” Design for NSCLC

NCI Thoracic Malignancy Steering Committee (TMSC) Task Force

- Early Stage NSCLC (ALCHEMIST)
- Advanced Stage NSCLC
  - Non-Squamous

Friends of Cancer Research (FOCR) Task Force

- Advanced Stage NSCLC
  - Squamous (SCCA):
    - SCCA represents an Unmet Need
      - All recent new targeted therapies have been in Adenoca (EGFR/ALK)
      - Many new molecular targets have been found in lung SCCA
      - Drugs for each of these targets
Selection of Therapeutic Targets for SCCA

- **Candidate targets** are available from results of TCGA project and other studies, identified by a **biomarker**
- **Drugs** (investigational) are now available for many of these targets
- Trials can be designed to **allow testing of multiple new drug-biomarker combinations at the same time** ("MASTER PROTOCOL" concept)

### Therapeutic targets
<table>
<thead>
<tr>
<th>Gene</th>
<th>Event Type</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>CDKN2A</td>
<td>Deletion/Mutation/Methylation</td>
<td>72%</td>
</tr>
<tr>
<td>PI3KCA</td>
<td>Mutation</td>
<td>16%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation/Deletion</td>
<td>15%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>15%</td>
</tr>
<tr>
<td>EGFR</td>
<td>Amplification</td>
<td>9%</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>Amplification/Mutation</td>
<td>9%</td>
</tr>
<tr>
<td>CCND1</td>
<td>Amplification</td>
<td>8%</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>4%</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>4%</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>4%</td>
</tr>
<tr>
<td>FGFR2</td>
<td>Mutation</td>
<td>3%</td>
</tr>
</tbody>
</table>
**MASTER PROTOCOL (SWOG): Squamous Lung Cancer - 2nd Line Therapy**

Biomarker Profiling (NGS/CLIA)

Multiple Phase II-III Arms with “rolling Opening & Closure

Biomarker A

Biomarker B

Biomarker C

Biomarker D

CT* Non-Match Drug

TT = Targeted therapy, CT = chemotherapy (docetaxel or gemcitabine), E = erlotinib

PI: V. Papadimitrakopoulou (SWOG)
Organizers: FOCR, NCI-TMSC, FDA, FNIH
Participants: Entire North American Lung Intergroup (SWOG, Alliance, ECOG-Acrin, NRG, NCI-Canada)
Screening: 500-1,000 patients/year
With 4-6 arms open simultaneously, anticipate a “hit rate ~70% in matching a patient with a drug/biomarker arm
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- Recognition of **lung cancer complexity** at the genomic level
  - including **inter- and intra patient tumor heterogeneity**
- Integration of this genomic complexity into **clinical decision-making process**
- Integration of this genomic complexity into **biomarker-driven drug development & clinical trial designs**
Models for Inter- and Intra-Patient Tumor Heterogeneity

Traditional View

Inter-patient Tumor Heterogeneity

Intra-patient Tumor Heterogeneity

Evolution over time

adapted from Gandara et al: Clin Lung Cancer, 2012
• **Intra-tumor heterogeneity** is present at baseline (scenarios 1 & 2)
• Reducing sensitive clones by therapy permits unopposed growth of less fit resistant clones or emergence of a new clone (“Tumor Darwinism”)
• Separating “new drivers” from “passengers” is complex
• This process is dynamic, not static
• Original sensitive clone is still present at time of resistance

 adapted from Gandara et al: Clin Lung Cancer, 2012
Approaches to Acquired Resistance in Oncogene-driven Cancers (EGFR MT & ALK Fusion)

Advanced NSCLC with Oncogene-driven Cancer
- EGFR Mutation
- ALK Fusion

Targeted TKI

RECIST Response
Subsequent Systemic PD

Switch Therapy
(Chemotherapy or 2nd gen TKI)

Continue same TKI alone
(to “slow progression”)?

Add Therapy to TKI
- Chemotherapy?
- Another Targeted Agent?

Re-biopsy

Systemic-PD

Baseline
Remission
Multiple PD Lesions

Gandara et al: Clin Lung Cancer 2013
Approaches to Acquired Resistance in Oncogene-driven Cancers (ALK Fusion)

Advanced NSCLC with Oncogene-driven cancer
ALK Fusion

ALK TKI (Crizotinib)

RECIST Response
Subsequent Systemic PD

Switch Therapy
Chemotherapy or 2nd gen TKI

Add Therapy to TKI
ALK TKI + Chemotherapy?

Re-biopsy

Gandara et al: Clin Lung Cancer 2013
Emergence of ALK Resistance Mechanisms after Crizotinib

- Secondary resistance ALK mutations
- ALK Gene copy number increase
- Transition to EGFR mutation
- Transition to KRAS mutation

Consistent with mathematical models of Evolutionary Biology

Doeble, Camidge et al: CCR 2012
S1300: Proposed SWOG/Intergroup Phase II Trial in ALK-positive NSCLC progressive after Crizotinib

**Primary Endpoints:**
1) PFS overall + 2) ORR in Pemetrexed arm

**Secondary:**
ORR, DCR, OS
Patterns of Failure
Toxicity
Translational Studies (Mechanisms of resistance)

**Pls:**
R. Camidge, T. Li & R. Doebele

**ALK dominant mechanisms of resistance**

- Resistance Mutations
- Copy Number Gain

**ALK non-dominant mechanisms of resistance**

- Second Oncogene (partially ALK dependent)
- Separate Oncogene (ALK-independent)

**Crizotinib**

Pemetrexed

30% Biopsy each arm

**Patterns of Failure**

**Translational Studies**
(Mechanisms of resistance)
PROFILE OO7: Crizotinib vs Chemotherapy in ALK+ NSCLC

**Primary Endpoint: PFS**

- **Crizotinib** (n=173)
  - Events, n (%): 100 (58)
  - Median, mo: 7.7
  - HR (95% CI): 0.49 (0.37 to 0.64)
  - P

- **Chemotherapy** (n=174)
  - Events, n (%): 127 (73)
  - Median, mo: 3.0

**PFS of Crizotinib vs Pemetrexed or Docetaxel**

- **Crizotinib** (n=172²)
  - Events, n (%): 100 (58)
  - Median, mo: 7.7
  - HR² (95% CI): 0.59 (0.43 to 0.89)
  - P: 0.0004

- **Pemetrexed** (n=95⁵)
  - Events, n (%): 72 (73)
  - Median, mo: 4.2
  - HR (95% CI): 0.30 (0.21 to 0.43)
  - P: <0.0001

- **Docetaxel** (n=72⁵)
  - Events, n (%): 54 (75)
  - Median, mo: 2.6

**Interim Analysis of OS**

- **Crizotinib** (n=173)
  - Events, n (%): 49 (28)
  - Median, mo: 20.3
  - HR (95% CI): 1.02 (0.88 to 1.54)\(^b\)
  - P: 0.5394

- **Chemotherapy** (n=174)
  - Events, n (%): 47 (27)
  - Median, mo: 22.8

---

*Shaw et al: ESMO 2012*
Approaches to Acquired Resistance in Oncogene-driven Cancers (EGFR Mutation)

Advanced NSCLC with Oncogene-driven Cancer
- EGFR Mutation

Targeted TKI

RECIST Response
Subsequent Systemic PD

Switch Therapy (Chemotherapy or 2nd gen TKI)

Continue same TKI alone (to “slow progression”)

Add Therapy to TKI
- Chemotherapy?
- Another Targeted Agent?

Re-biopsy

Gandara et al: Clin Lung Cancer 2013
Clinical Trial Designs to address **Circumvention of Acquired Resistance** in Oncogene-Driven NSCLC

Oncogene-driven NSCLC

Advanced Stage NSCLC → Biopsy → Identification of Driver Oncogene → EGFR Mutation

- Targeted TKI Monotherapy (Standard of Care)
- Targeted TKI Monotherapy (2nd generation agent)
- Multi-drug Targeted Therapy

Prolongation of Remission (delay time to PD)

*Gandara et al: Clin Lung Cancer 2013*
Approaches to Circumvention of Acquired Resistance in Oncogene-Driven NSCLC

Oncogene-driven NSCLC

Advanced Stage NSCLC

Biopsy

Identification of Driver Oncogene

EGFR Mutation

Targeted TKI Monotherapy (Standard of Care)

Targeted TKI Monotherapy (2nd generation agent)

Multi-drug Targeted Therapy

Prolongation of Remission (delay time to PD)

Gandara et al: Clin Lung Cancer 2013
Mechanisms of EGFR TKI Resistance (Selected)

- **Secondary EGFR mutation (i.e. T790m)**
  - $2^{nd}$ Gen EGFR TKIs
    - i.e. Afatinib
    - or Afatinib/Cetuximab

- **Bypass signaling via ERBB3**
  - Anti-ERBB3 drugs
    - i.e. MM151 MoAB

- **MET over-expression**
  - MET Inhibitors
    - i.e. MET-Mab (MoAB)
    - ARQ197 (TKI)

- **PIK3CA Mutation/AKT**
  - i.e. BKM120 (PIK3CA)
  - i.e. MK2206 (AKT)

  & Others
  - HSP inhibitors
    - i.e. Ganetespib
    - AUY922

adapted from Engelman et al
Trial of Afatinib-Cetuximab in EGFR MT+ NSCLC with acquired resistance to Erlotinib:

Tumor Regression by T790M Mutation Status

- What is the mechanism of action of this combination by comparison to Afatinib alone? (Afatinib alone~10%)
- How does cetuximab modify the activity of Afatinib?
- What are the mechanisms of resistance to this combination?

Overall RECIST Response Rate~38%

Proposed Phase III trials: Afatinib +/- Cetuximab in EGFR mutation+ NSCLC (North American Intergroup)

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**Stage IIIB-IV Adenocarcinoma with EGFR mutation+**

1st Line EGFR TKI naive

**Afatinib**

**Afatinib + Cetuximab**

*at PD: Biopsy for genomic study & PDX development (optional)

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**Stage IIIB-IV Adenocarcinoma with EGFR mutation+**

EGFR TKI pre-treated & resistant

**Afatinib**

**Afatinib + Cetuximab**

---

**PI:**

Lynch (SWOG-coordinated)

**PI:**

Pao (ECOG-coordinated)
Lung Cancer Treatment in 2020?

"Here's my sequence.
Please give me my cocktail."

The New Yorker