“Evolution” of Personalized Therapy Strategies for Advanced Non-Small Cell Lung Cancer (NSCLC)

David R. Gandara, MD
University of California Davis
Comprehensive Cancer Center
Disclosures

- Research Grants: AstraZeneca, BMS, Clovis, Genentech, JNJ, Lilly, Merck, Novartis
- Consultant: Ariad, AstraZeneca, Boehringer-Ingelheim, Celgene, Clovis, Genentech, Guardant Health, Lilly, Liquid Genomics, Merck, Mirati, Novartis, Peregrine, Pfizer, Synta
Theme: “Evolution” in NSCLC for 2016

- Evolution in Advanced NSCLC Therapeutic Landscape
- Evolution in Biomarker Testing Guidelines
- Evolution in understanding Mechanisms of Resistance to Therapy
- Evolution in Assessing Changes in Tumor Biology: Biopsy-Rebiopsy Strategies & Role of Plasma cfDNA
### Patients with Advanced Stage NSCLC (PS 0-1)

<table>
<thead>
<tr>
<th></th>
<th>Non-squamous</th>
<th>Squamous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong></td>
<td><strong>TKI (targeted therapy)</strong></td>
<td><strong>Chemo doublet +/- Bev</strong></td>
</tr>
<tr>
<td>1st line</td>
<td>EGFR MT</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>Non-Oncogene-Directed</td>
<td></td>
</tr>
<tr>
<td>2nd line</td>
<td>Chemo +/- TKI</td>
<td>Chemo</td>
</tr>
<tr>
<td>3rd line</td>
<td>Chemo</td>
<td>Chemo</td>
</tr>
</tbody>
</table>

**Gandara et al:** *Clin Lung Cancer (adapted)*
## Compartamental Treatment Paradigm:
### September 2016

**Patients with Advanced NSCLC (PS 0-1)**

<table>
<thead>
<tr>
<th></th>
<th>Non-squamous</th>
<th>Squamous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oncogene-Driven</td>
<td>PD-L1+</td>
</tr>
<tr>
<td><strong>1st line</strong></td>
<td>TKI (targeted therapy)</td>
<td>Checkpoint</td>
</tr>
<tr>
<td></td>
<td>EGFR, ALK, ROS1</td>
<td></td>
</tr>
<tr>
<td><strong>1st line Maintenance</strong></td>
<td>TKI</td>
<td>Checkpoint</td>
</tr>
<tr>
<td></td>
<td>3rd-gen TKI</td>
<td>Checkpoint</td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td>3rd-gen TKI</td>
<td>Chemo (± Ramu)</td>
</tr>
<tr>
<td></td>
<td>Chemo doublet</td>
<td></td>
</tr>
<tr>
<td><strong>3rd line</strong></td>
<td>Chemo doublet</td>
<td>Chemo</td>
</tr>
<tr>
<td></td>
<td>Checkpoint</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chemo</td>
<td></td>
</tr>
</tbody>
</table>

*Checkpoint does not include ipilimumab

Gandara et al: Clin Lung Cancer (adapted)
SQUIRE: Chemotherapy ± Necitumumab in Advanced Squamous Lung Cancer

1093 patients
- First-line Stage IV sq-NSCLC
- ECOG PS 0-2

Stratified HR (95% CI)
GC + N: 0.84 (0.74, 0.96)
GC: 1.00

Stratified P value (log-rank)
GC + N: 0.01
GC: 1.00

OS (months)
GC + N: 11.5 (10.4, 12.6)
GC: 9.9 (8.9, 11.1)

CR, complete response; GC, gemcitabine-cisplatin; N, necitumumab; OS, overall survival; PD, progressive disease; PR, partial response; R, randomization; SD, stable disease

Overall Survival in Patients With EGFR FISH Positive Squamous Lung Cancers treated with EGFR MoABs plus Chemotherapy

These data suggest that a biomarker strategy can be developed for EGFR MoAB-based therapies in Squamous Lung Cancer that will enhance efficacy.

FISH, fluorescent in situ hybridization; GC, gemcitabine and cisplatin; N, necitumumab
Strategies for Optimizing Development of New Therapies:
Single Agents vs Combinations vs Sequential (e.g. PD-1/PD-L1 agents)

- Single Agent: PD-L1
- Combo: PD-L1 + Platinum Chemo
- Combo: PD-L1 + Targeted Therapy (EGFR)
- Sequential: PD-L1 + Maintenance
- Sequential: Targeted Therapy or Chemo + PD-L1

adapted from Gandara et al: IASLC APLCC 2016
Phase III Trials of PD-1 therapy compared to Docetaxel in 2nd/3rd-Line Advanced/Metastatic NSCLC

"All comers" Strategy: (PD-L1+ & PD-L1-)

- Nivolumab Phase III Trials
  - Stage IIIIB/IV Squam (017) NSCLC
  - non-squamous (057) NSCLC

Nivolumab Phase III Trials
- Nivolumab 3 mg/kg IV Q2W

Docetaxel 75 mg/m² IV Q3W

Treat until progression or unacceptable toxicity or withdrawal of consent

Overall Survival (OS)

CheckMate 017: Squamous
CheckMate 057: Non-Squamous

Marker positive Strategy: PD-L1+

Pembrolizumab Phase III Trial
- Stage IIIIB/IV NSCLC

Pembrolizumab Phase III Trial
- Pembrolizumab 10 mg/kg IV Q3W
- Pembrolizumab 2 mg/kg IV Q3W
- Pembrolizumab 75 mg/m² IV Q3W

Treat until progression or unacceptable toxicity or withdrawal of consent

Overall Survival (OS)

KEYNOTE 010: Squamous + Non-Squamous
Perspective on CheckMate Phase III Trials

Two positive randomized phase III trials of nivolumab vs. docetaxel, but very different “Kinetics of Survival Curves”

Trial 017: Squamous Cell

- Nivolumab: n = 135
- Docetaxel: n = 137
- mOS, mo (95% CI): Nivolumab 9.2 (7.3, 13.3), Docetaxel 6.0 (5.1, 7.3)
- # events: 86 for Nivolumab, 113 for Docetaxel
- HR = 0.59 (95% CI: 0.44, 0.79), P = 0.00025
- 1-yr OS rate: Nivolumab 42%, Docetaxel 24%

Trial 057: Non-Squamous Cell

- Nivolumab: N = 292
- Docetaxel: N = 290
- mOS, mo: Nivolumab 12.2, Docetaxel 9.4
- HR = 0.73 (95% CI: 0.59, 0.89; P = 0.0015
- 1-yr OS rate: Nivolumab 51%, Docetaxel 39%

Brahmer et al: NEJM 2015
Borghei et al: NEJM 2015

“Kinetics of Survival Curves (OS)”
Trial 017 SQ: Early & continuous separation
Trial 057 Non-SQ: Cross-over but subsequent separation
CheckMate 017: Nivolumab vs Docetaxel in Advanced Squamous NSCLC

Survival benefit of nivolumab was independent of PDL1 expression levels in Squamous lung cancer although trends favor PD-L1+ cohorts
CheckMate 057: Nivo vs. Doc in advanced Non-Squamous NSCLC

OS by PD-L1 Expression

OS benefit correlates with PD-L1 expression in this Non-SQ trial.
KEYNOTE-010: Pembrolizumab vs Docetaxel in Previously Treated, PD-L1-Positive NSCLC

- OS superior with pembrolizumab in all groups but most impressive in ≥50%
- PFS benefit was superior in ≥50%, but not significant for either Pembrol dose with PD-L1 ≥1%.

Herbst et al., Lancet. 2016;387:1540-1550
Phase III Study of Anti-PD-L1 agents compared to Platinum Chemotherapy in 1st-Line Advanced NSCLC (PD-L1+)

Only PD-L1+ are eligible
(Marker+ strategy in both trials)

**BMS-558 (Nivolumab)**
- **CheckMate 026** - Phase III Trial
  - Stage IIIB/IV NSCLC
  - N=495
- **Platinum Doublet** Q3W
- **Nivolumab 3 mg/kg IV Q2W**
- **NEGATIVE**
- **Progression Free Survival (PFS)**

**MK-3475 (Pembrolizumab)**
- **KeyNote 024** - Phase III Trial
  - Stage IIIB/IV NSCLC
  - N=300
- **Platinum Doublet Q3W**
- **MK-3475 200 mg IV Q3W**
- **POSITIVE**
- **Progression Free Survival (PFS)**
KEYNOTE-024: Pembro vs Chemotherapy in 1st-line therapy of Advanced NSCLC

KEYNOTE-024 Studied Patients Whose Tumors Expressed High Levels of PD-L1

KENILWORTH, N.J., June 16, 2016 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the KEYNOTE-024 trial investigating the use of KEYTRUDA® (pembrolizumab), in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint. In this trial, KEYTRUDA was superior compared to chemotherapy for both the primary endpoint of progression-free survival (PFS), and the secondary endpoint of overall survival (OS). Based on these results, an independent Data Monitoring Committee (DMC) has recommended that the trial be stopped, and that patients receiving chemotherapy in KEYNOTE-024 be offered the opportunity to receive KEYTRUDA.

- This trial will alter the SOC in 1st-line therapy of patients with advanced NSCLC
- It confirms that this IO approach qualifies as “targeted therapy” using the PD-L1 biomarker
CHECKMATE 026: Nivolumab vs Chemotherapy in 1st-line therapy of Advanced NSCLC

August 5, 2016, 8:20 am EDT

Bristol-Myers Squibb Announces Top-Line Results from CheckMate -026, a Phase 3 Study of Opdivo (nivolumab) in Treatment-Naïve Patients with Advanced Non-Small Cell Lung Cancer

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) announced today that CheckMate -026, a trial investigating the use of Opdivo (nivolumab) as monotherapy, did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed PD-L1 at ≥ 5%. The company will complete a full evaluation of the CheckMate -026 data and work with investigators on the future presentation of the results.

CHECKMATE 026 did not meet primary endpoint of improved PFS
In NSCLC with PD-L1+ at 5% level
These results confirm that biomarkers matter for PD-1 agents
& that PD-L1 is clinically relevant in advanced NSCLC
Theme: “Evolutions” in NSCLC for 2016

- Evolution in Advanced NSCLC Therapeutic Landscape
- Evolution in Biomarker Testing Guidelines
- Evolution in understanding of Mechanisms of Resistance to Therapy
- Evolution in Assessing Changes in Tumor Biology: Biopsy-Rebiopsy Strategies & Role of Plasma cfDNA
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
- **What specimen?:** core needle biopsy (or multi-pass FNA), cytology cell block, surgical biopsy (bone biopsy problematic)

Updated Guidelines Pending 2016
Awaiting public commentary
Include incorporation of Next Generation Sequencing (NGS)

Evolution of NSCLC Subtyping from Histologic to a Multitude of Genomically-defined Subsets

NSCLC as one disease

Histology-based Subtyping

Adenocarcinoma

Squamous Cell Cancer

Initial oncogene mutation-targeted therapies

ALK

EGFR

Li, Mack, Kung, Gandara: JCO 2013
Evolution of Biomarker Testing in Clinical Practice: Past, Current & Future

1. Histomorphological Diagnosis: Cancer

2. Molecular Diagnosis:
   - Extract tumour 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

Plasma cf DNA by NGS

From Li, Gandara et al. JCO. 2013.
# The Growing List of Guideline Recommendations for Molecular Testing

**Non-Small Cell Lung Cancer**

### Targeted Agents for Patients with Genetic Alterations

<table>
<thead>
<tr>
<th>Genetic Alteration (ie, Driver event)</th>
<th>Available Targeted Agents with Activity Against Driver Event in Lung Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR mutations</td>
<td>erlotinib(^1), gefitinib(^2), afatinib(^3)</td>
</tr>
<tr>
<td>ALK rearrangements</td>
<td>crizotinib(^4), ceritinib(^5)</td>
</tr>
<tr>
<td>HER2 mutations</td>
<td>trastuzumab(^6), afatinib(^7)</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>vemurafenib(^8), dabrafenib(^9)</td>
</tr>
<tr>
<td>MET amplification</td>
<td>crizotinib(^10)</td>
</tr>
<tr>
<td>ROS1 rearrangements</td>
<td>crizotinib(^11)</td>
</tr>
<tr>
<td>RET rearrangements</td>
<td>cabozantinib(^12)</td>
</tr>
</tbody>
</table>

Note: EGFR mutations too rare (<3.6%) to be routinely tested in squamous cell carcinoma

Translating Genomic Profiling Data into Therapeutic Strategies
(Lung Adenocarcinoma)

**RETT:** Cabozantinib: RR=40%

**ALK:** 65% RR to Crizotinib; ~70% RR to 2° Gen TKI Ceritinib in resistant cancers

**METex14:**
- RR >50% to Crizotinib
- ~70% RR to 2° Gen TKI Ceritinib in resistant cancers

**ROS1:**
- 70% RR to Crizotinib

**HER2 mutation:**
- >50% RR to Afatinib
- ~20% to Dacomitinib

**BRAF (V600E):**
- >60% RR to BRAF + MEK inhibitor combo

**KRAS:**
- 35% RR to MEK inhibitors + Chemotherapy

**EGFR:**
- RR>70% to 1°-2° Gen TKIs; 
  - ~60% RR to 3° Gen TKIs in resistant cancers
# Sensitivity & Breath of different Technologies for EGFR mutation detection in tissue

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Mutations Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct sequencing</td>
<td>25%</td>
<td>Known and new</td>
</tr>
<tr>
<td>PCR-SSCP</td>
<td>10%</td>
<td>Known and new</td>
</tr>
<tr>
<td>TaqMan PCR</td>
<td>10%</td>
<td>Known only</td>
</tr>
<tr>
<td>Loop-hybrid mobility shift assay</td>
<td>7.5%</td>
<td>Known only</td>
</tr>
<tr>
<td>Cycleave PCR</td>
<td>5%</td>
<td>Known only</td>
</tr>
<tr>
<td>PCR-RLFP (fragment length analysis)</td>
<td>5%</td>
<td>Known only</td>
</tr>
<tr>
<td>MassARRAY genotyping</td>
<td>5%</td>
<td>Known only</td>
</tr>
<tr>
<td>LNA-PCR clamp</td>
<td>1%</td>
<td>Known only</td>
</tr>
<tr>
<td>Scorpion ARMS (DxS)</td>
<td>1%</td>
<td>Known only</td>
</tr>
<tr>
<td>dHPLC</td>
<td>1%</td>
<td>Known only</td>
</tr>
<tr>
<td>COLD-TaqMan PCR</td>
<td>0.05%</td>
<td>Known only</td>
</tr>
<tr>
<td>Parallel (Next Generation) Sequencing</td>
<td>0.01%</td>
<td>Known and Unknown</td>
</tr>
</tbody>
</table>

SSCP, single-strand conformation polymorphism; RLFP, restriction fragment length polymorphism; LNA, locked nucleic acid; ARMS, Amplification Refractory Mutation System; dHPLC, denaturing high performance liquid chromatography

EGFR E19del mutations detected by NGS in cases previously negative by other molecular testing techniques

Table 2. Characteristics of cases with prior negative EGFR test results

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>EGFR mutation detected by CGP</th>
<th>Previous EGFR test result</th>
<th>Same specimen tested by prior EGFR assay and CGP</th>
<th>Additional genes negative by hotspot testing</th>
<th>Response to EGFR targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>S752_L759del</td>
<td>Negative</td>
<td>N</td>
<td>ALK</td>
<td>na</td>
</tr>
<tr>
<td>2</td>
<td>T750_L759&gt;NLD</td>
<td>Negative</td>
<td>na</td>
<td>ALK, KRAS, PIK3CA</td>
<td>na</td>
</tr>
<tr>
<td>3</td>
<td>T751_L759&gt;N</td>
<td>Negative</td>
<td>Y</td>
<td>ALK, ROS1</td>
<td>PR, afatinib</td>
</tr>
<tr>
<td>4</td>
<td>T751_L760&gt;NL</td>
<td>Negative</td>
<td>N</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>5</td>
<td>T751_L760&gt;NL</td>
<td>Negative</td>
<td>Y</td>
<td>ALK</td>
<td>na</td>
</tr>
<tr>
<td>6</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>Y</td>
<td>ALK, KRAS</td>
<td>PR, erlotinib</td>
</tr>
<tr>
<td>7</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>Y</td>
<td>ALK, ROS1</td>
<td>na</td>
</tr>
<tr>
<td>8</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>N</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>9</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>N</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>10</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>Y</td>
<td>KRAS</td>
<td>na</td>
</tr>
<tr>
<td>11</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>N</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>12</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>Y</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>13</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>Y</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>14</td>
<td>E746_A750del</td>
<td>Negative</td>
<td>Y</td>
<td>ALK, KRAS</td>
<td>*afatinib</td>
</tr>
<tr>
<td>15</td>
<td>L747_A750&gt;P</td>
<td>Negative</td>
<td>Y</td>
<td>ALK, KRAS, BRAF</td>
<td>na</td>
</tr>
<tr>
<td>16</td>
<td>L747_A750&gt;P</td>
<td>Negative</td>
<td>N</td>
<td></td>
<td>na</td>
</tr>
<tr>
<td>17</td>
<td>L747_K754&gt;G</td>
<td>Negative</td>
<td>Y</td>
<td>ALK, KRAS</td>
<td>na</td>
</tr>
</tbody>
</table>

Sherock, Peled et al.  
Clin Cancer Res. 2016
Theme: “Evolutions” in NSCLC for 2016

- Evolution in Advanced NSCLC Therapeutic Landscape
- Evolution in Biomarker Testing Guidelines
- Evolution in understanding of Mechanisms of Resistance to Therapy
- Evolution in Assessing Changes in Tumor Biology: Biopsy-Rebiopsy Strategies & Role of Plasma cfDNA
Targeted Therapies in Oncogene-Driven NSCLC: De Novo & Acquired Resistance

- **Targeted Therapies** against Oncogene-Driven Cancers, EGFR mutation+ (Erlotinib) or ALK fusion+ (Crizotinib), improve response and PFS when compared with chemotherapy.
- Even in these most sensitive cancers, approximately 25% to 40% do not respond to TKI therapy *(de novo resistance)*.
- Even in these most sensitive cancers, acquired resistance is ~universal, with PFS averaging ~10-14 months.

*Gandara et al: Clin Lung Cancer 2014*
Mechanisms of Acquired Resistance to EGFR TKIs in EGFR-mutated Lung Cancers

- At the time of acquired resistance, **T790M** is found in over 50% of repeat biopsies.\(^1\)
- **T790M** may not always be the cause of clinical resistance, even when present.
- Several **bypass mechanisms** of resistance, including MET or HER2 amplification, or PIK3CA or BRAF mutation, have now been identified.
- **SCLC transformation** can also occur, but is uncommon-rare.

*Camidge et al., Nature Rev Clin Oncol, 2014*
Even in the subset of EGFR-mutated cancers with T790M+ acquired resistance, approximately 30% do not achieve RECIST response.

In about 5-10%, the best response is Progressive Disease (PD).

How can we enhance the efficacy of an already effective drug (Osimertinib)?

- Increase the rate of complete response?
- Delay onset of resistance?
- Increase the proportion of patients on the tail of the survival curve?
ETCTN Project Team Proposals: AZD9291 in EGFR-mutated NSCLC post-progression after Erlotinib

**Trial 1**
- AZD9291 + Necitumumab
- Dose escalation 3+3 design
- Expansion cohorts
- \( T^{790M}\)-ve expansion cohort at MTD (n=12)

**Trial 2**
- AZD9291 + navitoclax
- \( T^{790M}\)+ resistance to initial EGFR TKI (n=20)

**Trial 3**
- AZD9291 + MLN-0128
- \( T^{790M}\)-ve expansion cohort at MTD (n=12)
Theme: “Evolutions” in NSCLC for 2016

• Evolution in Advanced NSCLC Therapeutic Landscape
• Evolution in Biomarker Testing Guidelines
• Evolution in understanding of Mechanisms of Resistance to Therapy
• Evolution in Assessing Changes in Tumor Biology: Biopsy-Rebiopsy Strategies & Role of Plasma cfDNA
Schema for Multidisciplinary Integration of Biomarker Testing in Advanced Stage NSCLC: Looking for “Actionable” Oncogenes

1. Identify Patient
2. Identify Target Lesion
3. Pulmonologist Interventional Radiologist
4. Biopsy
5. Histology Evaluation
6. Molecular Biomarker Testing
7. When Progression → Re-Biopsy
8. Determine New Therapy
9. When Progression → Re-Biopsy

Adapted from: Raez, Gandara et al Clin Lung Cancer 2016
Mechanisms of EGFR TKI Resistance & Potential Therapeutic Approaches (Selected)

- Secondary EGFR mutation (i.e. T790M)

  - 2nd Gen EGFR TKIs i.e. Afatinib/Cetuximab
  - 3rd Gen- AZD9291, CO1686

- Bypass signaling via ERBB2

  - Anti-ERBB2 drugs i.e. Afatinib, Dacomitinib

- MET over-expression

  - MET Inhibitors i.e. Crizotinib, Salulitinib

- PIK3CA Mutation/AKT

  - i.e. BKM120 (PIK3CA)
  - i.e. MK2206 (AKT)
  & Others

  - HSP inhibitors i.e. Ganetespib, Onalespib

Schema for Multidisciplinary Integration of Biomarker Testing in Advanced Stage NSCLC: Looking for “Actionable” Oncogenes

- Referring Physician
  - Identify Patient
  - Multidisciplinary Team (Tumor Board)
    - Identify Target Lesion
    - Med Oncologist
    - Thoracic Surgeon
    - Radiation Oncologist
  - Pulmonologist
  - Interventional Radiologist
  - Surgeon

- Biopsy
- Histology Evaluation
- Molecular Biomarker Testing

- Pathologist

- Oncologist
  - Determine Therapy
  - Treat
  - When Progression
    - Plasma cfDNA
    - Treat

- When Progression
  - Determine New Therapy
  - Treat
  - Plasma cfDNA

Adapted from: Raez, Gandara et al Clin Lung Cancer 2016
Role of “Liquid Biopsy” (Plasma cf DNA) in determining mechanisms of Acquired Resistance

Advantages of plasma cf DNA over Tumor re-biopsy
- Relatively non-invasive
- Provides “global” perspective, abrogating issue of tumor heterogeneity
- Can be repeated serially over time to monitor tumor response
- Can detect resistance mutations in plasma prior to radiographic detection

from Burrell and Swanton, Mol Oncol 2014
Association between plasma EGFR mut+ at Cycle 3 and PFS/OS (from FASTACT Trial)

**PFS**
- C3 mut+
- C3 mut–
- Median = 7.2 months (95% CI: 6.0–7.8)
- Median = 12.0 months (95% CI: 9.6–16.5)
- HR = 0.32 (95% CI: 0.21–0.48); P<0.0001

**OS**
- C3 mut+
- C3 mut–
- Median = 18.2 months (95% CI: 14.2–27.4)
- Median = 31.9 months (95% CI: 23.5–undefined)
- HR = 0.51 (95% CI: 0.31–0.84); P=0.0066

**Patients, n**
- C3 mut+
- C3 mut–

**Mok et al. Clin Ca Res 2015**
Plasma ctDNA utility in under-genotyped NSCLC

Tissue Genotyping Status (n=362 non-squamous NSCLC)

- Tissue Biomarker Positive (n=120, 33%)
- Tissue QNS / Partially Genotyped (n=229, 63%)
- Tissue NGS, Biomarker Negative (n=13, 4%)

- 4% of tissue samples are biomarker positive.
- 63% of tissue samples are QNS or partially genotyped.
- 4% of tissue samples are biomarker negative.

ctDNA NGS Increased Biomarker Yield by 42% (51 additional biomarkers identified in tissue QNS/PG cases)

- Tissue Biomarker Positive (n=120, 33%)
- ctDNA Biomarker Positive in Tissue QNS/PG (n=51, 14%)
- Tissue QNS/PG, ctDNA Biomarker Neg (n=178, 49%)
- Tissue NGS, Biomarker Negative (n=13, 4%)

- 4% of ctDNA samples are biomarker positive.
- 33% of ctDNA samples are biomarker positive in tissue QNS/PG.
- 14% of ctDNA samples are biomarker negative in tissue QNS/PG.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>N in Tissue</th>
<th>Biomarker</th>
<th>N in Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>98</td>
<td>RET fusion</td>
<td>1</td>
</tr>
<tr>
<td>KRAS</td>
<td>11</td>
<td>BRAF&lt;sup&gt;V600E&lt;/sup&gt;</td>
<td>1</td>
</tr>
<tr>
<td>ALK fusion</td>
<td>5</td>
<td>MET/ERBB2 amp</td>
<td>2</td>
</tr>
<tr>
<td>ROS1 fusion</td>
<td>2</td>
<td>TOTAL</td>
<td>120</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>N in ctDNA*</th>
<th>Biomarker</th>
<th>N in ctDNA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>8</td>
<td>RET fusion</td>
<td>3</td>
</tr>
<tr>
<td>KRAS</td>
<td>28</td>
<td>BRAF&lt;sup&gt;V600E&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>ALK fusion</td>
<td>1</td>
<td>MET/ERBB2 amp</td>
<td>7</td>
</tr>
<tr>
<td>ROS1 fusion</td>
<td>0</td>
<td>TOTAL</td>
<td>51</td>
</tr>
</tbody>
</table>

*among Tissue QNS/PG

Gandara et al: IASLC LALCA 2016
Phase II/III Trial of Afatinib With or Without Cetuximab in 1st-Line Therapy of EGFR-mutated NSCLC (S1403)

PIs: Goldberg, Lilenbaum, Politi.

Stage IIIB-IV NSCLC with EGFR mutation (E19del, L858R) 1st Line EGFR TKI naive

Genomics analysis (NGS) + cfDNA analysis

Afatinib*

Afatinib + Cetuximab*

*at PD: Biopsy for tumor & cfDNA genomics & PDX development (selected patients)

PD: progressive disease

PDX: patient-derived xenograft
Summary: “Evolution” in NSCLC for 2016

- Evolution in Advanced NSCLC Therapeutic Landscape
- Evolution in Biomarker Testing Guidelines
- Evolution in understanding of Mechanisms of Resistance to Therapy
- Evolution in Assessing Changes in Tumor Biology: Biopsy-Rebiopsy Strategies & Role of Plasma cfDNA