Novel Treatment for Lung Cancer

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Novel Strategies to Personalize Therapy in Advanced Non-Small Cell Lung Cancer (NSCLC)

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Comprehensive Cancer Center
Disclosures

• Research Grants: AZ/Medi, BMS, Clovis, Genentech, JNJ, Lilly, Merck, Novartis

• Consultant: AstraZeneca, Boehringer-Ingelheim, Celgene, Clovis, Genentech, Guardant Health, Lilly, Merck, Novartis, Perigrine, Pfizer, Response Genetics, Synta
“Eating an Elephant: An analogy to defeating Lung Cancer

“If you want to eat an elephant, you need a strategy”

“If you try to do it in one bite, you will choke on it”

M. Vestager. – May 25, 2015
EU Antitrust Chief
& Danish politician

“When eating an elephant, take 1 bite at a time”
Creighton Adams, Jr, General Chief of Staff, US Army 1972
Requisites: Transition from Empiric to Personalized Cancer Therapy (Biomarker-Driven)

Empiric Therapy → Biomarker-Driven & Personalized Therapy

- Tumor Molecular Profiling to identify drug targets (adequate tumor tissue)
- Drugs against the Molecular Targets
- Predictive Biomarkers for the drugs
- Clinical Trial Designs that define the activity of a drug against its target (predictive biomarker)

What are the available “Tools” to facilitate Individualized Therapy in advanced stage NSCLC?

**Chemotherapy**

- **Histologic Subtyping for Chemotherapy**

**“Targeted Therapy”**

- Anti-PD-1 and PD-L1 (Anti-CTLA-4)?
- Genomics-driven TKIs: -EGFR -ALK -ROS1

**Checkpoint Immunotherapy**

The Questions: How do we optimize therapy in individual patients? How do we account for tumor evolution over time and after targeted therapy? How do we best integrate new diagnostic testing platforms for targeted therapy or immunotherapy to achieve optimal results? (Next Gen Sequencing [NGS] in tissue or cell free[cf]DNA in plasma)
Evolution of NSCLC Subtyping from Histologic to a Multitude of Genomically-defined Subsets

What does this mean from the Patient and Physician standpoint?

100 patients with advanced stage Lung Cancer:
They all look alike, but they are not
100 patients with advanced stage Lung Cancer: Non-small Cell (NSCLC) versus Small Cell Lung Cancer (SCLC)
86 patients with advanced stage NSCLC: They all look alike, but they are not

In 2015:
• Oncologists would conclude that these patients have very different malignancies
• Oncologists would conclude that these patients have vastly different therapeutic options
86 patients with advanced stage NSCLC: Breakdown by Histologic Subtype

- **Adeno**
- **Large cell /NE**
- **SCC**
86 patients with advanced stage NSCLC:
Therapeutic Implications of Non-SCC versus SCC

Two therapeutic agents contraindicated in SCC:
- Pemetrexed: reduced efficacy in SCC
- Bevacizumab: increased toxicity in SCC
JMDB: Pemetrexed/Cisplatin vs Gemcitabine/Cisplatin in NSCLC with Pre-defined Analysis by Histologic Subtype

Pem/Cisplatin

- Previously Untreated
- Stage IIIB or IV
- ECOG PS 0-1
- N=1,725

Gem/Cisplatin

1. Adenocarcinoma
2. Large Cell
3. Squamous Cell

Scagliotti, Gandara et al. JCO 26: 3543, 2008
JMDB: Pemetrexed/Cisplatin vs Gemcitabine/Cisplatin in Advanced NSCLC

No differences between regimens in the overall patient population

Scagliotti, Gandara et al. JCO, 2008.
JMDB: Pemetrexed/Cisplatin vs Gemcitabine/Cisplatin in NSCLC with Pre-defined Analysis by Histologic Subtype

• Pemetrexed regimen superior in Non-squamous histology
• Gemcitabine regimen superior in Squamous histology

Scagliotti, Gandara et al. JCO, 2008.
Thymidylate Syntase (TS) mRNA expression by Histology: Squamous (SCCA) versus Adenocarcinoma (AC)

N=1,671

<table>
<thead>
<tr>
<th>TS</th>
<th>% Below Reference Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC-Total</td>
<td>42%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>46%</td>
</tr>
<tr>
<td>SCCA</td>
<td>26%</td>
</tr>
</tbody>
</table>

TS is a molecular target of Pemetrexed
High TS is indicative of Pemetrexed resistance
Thus SCCA is relatively resistant to Pemetrexed by comparison with Adenocarcinoma
However, TS remains a research tool (not fully validated)

60 patients with advanced stage NSCLC: Non-SCC Histology

Non-SCC  (Adeno+ Large Cell)
60 patients with advanced stage Non-SCC NSCLC: Breakdown by Oncogene Subtype

"The Big 3"

- EGFR
- ALK
- ROS1
- KRAS
- Adeno/Large Cell
‘Targeted’ Therapy is most effective when directed toward patients with cancers expressing the target: ‘Oncogenic Addiction’

<table>
<thead>
<tr>
<th>Target(s)</th>
<th>EGFR</th>
<th>EGFR</th>
<th>EGFR (~ErbB family)</th>
<th>ALK ROS1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Gefitinib (1st Gen)</td>
<td>Erlotinib (1st Gen)</td>
<td>Afatinib (2nd Gen)</td>
<td>Crizotinib (1st Gen)</td>
</tr>
<tr>
<td>Response (average)</td>
<td>~60-75%</td>
<td>~60-75%</td>
<td>~60-75%</td>
<td>~60-70%</td>
</tr>
<tr>
<td>Progression Free Survival</td>
<td>~10 months</td>
<td>~10 months</td>
<td>~11 months</td>
<td>~11 months</td>
</tr>
</tbody>
</table>
EGFR Mutations
About 12% of NSCLC
In US (40% in E. Asia)

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

But clinical characteristics are insufficient to select 1st line therapy

IPASS: Gefitinib vs Chemotherapy in East Asian Patients with Advanced Lung Adenocarcinoma

Eligibility
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage III B / IV disease

Endpoints

Primary
- Progression-free survival

Secondary
- Objective response rate
- Overall survival
- Quality of life/Toxicity

Exploratory
- EGFR mutation

*All East Asian
80% female
94% never-smokers

Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>609</td>
<td>608</td>
</tr>
<tr>
<td>Events</td>
<td>453 (74.4%)</td>
<td>497 (81.7%)</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.741 (0.651, 0.845) p<0.0001

Median PFS (months) 5.7 5.8
12 months progression-free 25% 7%

Mok et al: NEJM, 2009
IPASS* (TKI Gefitinib versus Chemotherapy): Impact of EGFR mutation

Progression-free survival in EGFR mutation positive & negative cancers

**EGFR mutation positive**

- Gefitinib (n=132)
- Carboplatin / paclitaxel (n=129)

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

**EGFR mutation negative**

- Gefitinib (n=91)
- Carboplatin / paclitaxel (n=85)

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

*All East Asian patients, 80% female, 94% never-smokers

- Clinical characteristics are insufficient for selection of 1st line EGFR TKI Therapy
- Front line EGFR TKI should be restricted to EGFR MT+ patients

The Growing List of Guideline Recommendations: Too Many Mutations for a Single Test

Non-Small Cell Lung Cancer

<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, gefitinib, afatinib</td>
</tr>
<tr>
<td>ALK rearrangements</td>
<td>crizotinib, ceritinib</td>
</tr>
<tr>
<td>HER2 mutations</td>
<td>trastuzumab, afatinib</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>vemurafenib, dabrafenib</td>
</tr>
<tr>
<td>MET amplification</td>
<td>crizotinib</td>
</tr>
<tr>
<td>ROS1 rearrangements</td>
<td>crizotinib</td>
</tr>
<tr>
<td>RET rearrangements</td>
<td>cabozantinib</td>
</tr>
</tbody>
</table>

Note: EGFR mutations too rare (<3.6%) to be routinely tested in squamous cell carcinoma
Evolution of Biomarker Testing in Clinical Practice: Past, Current & Future

1. Histomorphological Diagnosis: Cancer

2. Molecular Diagnosis:
   - Archival FFPE tumour specimens
   - Archival cancer specimens
   - Macro- or Micro-dissection of Tumours
   - Extract tumour nucleic acids:
     - DNA and RNA

   **Current Approach (Target-Based Therapy V1.0):** Single gene molecular testing for decision-making in individual patients

   **Evolving Approach (Target-Based Therapy V2.0):** Multiplexed molecular tests with increased sensitivity & output for decision-making in individual patients

   **Near-Future Approach (Patient-Based Therapy):** Genomic profiling by high throughput next generation sequencing for decision-making in individual patients

   **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

RET: Cabozantinib: RR=40%

ROS1: 70% RR to Crizotinib

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

METex14: RR >50% to Crizotinib

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

HER2 mutation:
- MET amp: (0.9%)
- RIT1: (2.2%)

ROS1 fusion: (1.7%)

ERBB2 (1.7%)

MET ex14

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

BRAF

KRAS

MEK inhibitors + Chemotherapy

KRAS: 35% RR to MEK inhibitors + Chemotherapy

EGFR: RR>70% to 1°-2° Gen TKIs; ~60% RR to 3° Gen TKIs in resistant cancers

EGFR

KRAS

HER2

ROS1

ALK

MET

ROS1

ERBB2

NF1

None

Translating Genomic Profiling Data into Therapeutic Strategies (Lung Adenocarcinoma)
Acquired Resistance to Targeted Therapies in Oncogene-Driven NSCLC: Clinical Practice & Clinical Trials

- **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, acquired resistance is ~universal,** with PFS averaging ~10-14 months
- **New strategies** are needed to address acquired resistance and/or to circumvent it

Cancer Evolution after Therapy (Acquired Resistance)

Major Clinical Implications
- Tumor sampling bias dependent on which site biopsy obtained
- Defining “actionable” mutations (“Driver” vs “Passengers”)?
- Defining mechanism of drug resistance after therapy?

Variations on Branched Evolution

Burrell and Swanton: Mol Oncol 2014 & CA Res 2012
Evolution of NSCLC Subtyping from Histologic to a Multitude of Genomically-defined Subsets: Emergence of Acquired Resistance after therapy

Li, Mack, Gandara et al. *JCO*. 2013 (adapted from Pao et al).
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

\(^{1}\) Camidge et al., Nature Rev Clin Oncol, 2014
Mechanisms of EGFR TKI Resistance & Potential Therapeutic Approached (Selected)

- Secondary EGFR mutation (i.e. T790M)
  - 2nd Gen EGFR TKIs i.e. Afatinib/Cetuximab
  - 3rd Gen- AZ9291, CO1686

- Bypass signaling via ERBB2
  - Anti-ERBB2 drugs i.e. Afatinib, Dacomitinib

- MET over-expression
  - MET Inhibitors i.e. Crizotinib, Salutitinib

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

& Others
  - HSP inhibitors i.e. Ganeespib, AUY922

Differential Response Rates by EGFR T790M status with AZD9291 but not Afatinib/Cetuximab

<table>
<thead>
<tr>
<th></th>
<th>Overall RR</th>
<th>T790M+ RR</th>
<th>T790M- RR</th>
<th>Overall PFS</th>
<th>T790M+ PFS</th>
<th>T790M- PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib--AZD9291&lt;sup&gt;1&lt;/sup&gt;</td>
<td>53%</td>
<td>59%</td>
<td>22%</td>
<td>NA</td>
<td>11.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Rociletinib-CO1686&lt;sup&gt;2&lt;/sup&gt;</td>
<td>NA</td>
<td>34%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Afatinib-Cetuximab&lt;sup&gt;3&lt;/sup&gt;</td>
<td>29%</td>
<td>32%</td>
<td>25%</td>
<td>4.7</td>
<td>4.6</td>
<td>4.8</td>
</tr>
</tbody>
</table>

NA: Not Available

2. J. Goldman. IASLC Targeted Therapies 2016 (revised)
Phase II/III Trial of Afatinib With or Without Cetuximab in 1st-Line Therapy of EGFR-mutated NSCLC (S1403): An Approach to Circumventing Acquired Resistance

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

Afatinib*
Afatinib + Cetuximab*

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

Genomics analysis (NGS) + cfDNA analysis

PD: progressive disease
PDX: patient-derived xenograft

PIs: Goldberg, Lilienbaum, Politi.
“Re-biopsy” Strategy for Biomarker Testing in Advanced Stage NSCLC: Looking for changes in “Actionable” Oncogenes

Referring Physician

Identify Patient

Multidisciplinary Team (Tumor Board)

Identify Target Lesion

Med Oncologist
Thoracic Surgeon
Radiation Oncologist
Pulmonologist
Radiologist
Pathologist

Pulmonologist Interventional Radiologist Surgeon

Biopsy

Histology Evaluation

Pathologist

Molecular Biomarker Testing

When Progression
Plasma cfDNA

Treat

Determine New Therapy

Oncologist

Determine Therapy

Treat

When Progression
Plasma cfDNA

Adapted from: Gandara: ASTRO/ASCO/IASLC Symposium on Molecular Testing, 2012
Role of “Liquid Biopsy” (Plasma cf DNA) in determining mechanisms of Acquired Resistance

Burrell and Swanton, Mol Oncol 2014
Case Example: Role of Liquid Biopsy in EGFR-Mutated NSCLC

- 50 y/o woman with EGFR-mutated adenocarcinoma (E19del)
- Previously treated with the EGFR TKI Erlotinib with good response for 1 year
- Now progressive disease (PD) in lung, liver and bones
- A repeat biopsy of a liver lesion is done to determine resistance mechanisms
- Molecular testing on the repeat biopsy shows the original Exon19del mutation but is negative for the resistance mutation T790M

Courtesy of Nir Piled (adapted)
Case Example: 50 y/o woman with EGFR-mutated lung cancer
At relapse after TKI, re-biopsy is negative for T790M.
The logical next treatment would then by chemotherapy, not a 3rd Gen EGFR TKI

Plasma Next Gen Sequencing for cell free (cf)DNA

Table 1. Allele frequency of altered circulating cell-free DNA detected in this patient

<table>
<thead>
<tr>
<th>Gene</th>
<th>% cfDNA</th>
<th>0.01%</th>
<th>0.1%</th>
<th>1%</th>
<th>10%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53 Q144*</td>
<td>24.19%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75.81%</td>
</tr>
<tr>
<td>EGFR T790M</td>
<td>6.49%</td>
<td>93.51%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR G724S</td>
<td>2.85%</td>
<td>97.15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF1 R1362*</td>
<td>1.85%</td>
<td>98.15%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR A688A</td>
<td>0.69%</td>
<td>99.31%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR G689*</td>
<td>0.68%</td>
<td>99.32%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF1 S1766*</td>
<td>0.37%</td>
<td>99.63%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR Exon 19 Del</td>
<td>19.51%</td>
<td></td>
<td></td>
<td>80.49%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend:
% cfDNA: Allele frequency of genomic alteration observed in this patient’s circulating cell-free DNA.
- : Cell-free DNA with alterations.
- : Cell-free DNA without alterations.
Del = Deletion

Courtesy of Nir Pelad & Guardant Health
Based on cfDNA analysis, patient started on clinical trial of 3rd gen EGFR TKI AZ9291
Repeat PET scan 2 weeks later: Major Response.

Lessons Learned:
• This is an example of intra-tumor heterogeneity
• Re-biopsy missed T790M; detected by plasma cfDNA
Role of Checkpoint Immunotherapy in Individualized Cancer Patient Care

- Cancer cells have mutations that make them recognizable by the immune system (neo-antigens).

- Theoretically, the higher the mutational load (e.g., through smoking), the greater the immune recognition.

- Cancer cells can evade immune surveillance by expressing proteins such as PD-L1 (a potential biomarker).

- Inhibiting PD-L1/PD-1 interaction can restore anti-tumor T-cell activity, leading to immune-mediated response.

Major PD-1/PD-L1 antagonists:
- Nivolumab (anti-PD-1)
- Pembrolizumab (anti-PD-1)
- Atezolizumab (MPDL3280A, anti-PD-L1)
- Durvalumab (MEDI-4736, anti-PD-L1)
- Avelumab (anti-PD-L1)
Spectrum of PD-1/PD-L1 Antagonist Activity

Active

- **Melanoma**
- **Renal cancer**
- **NSCLC – adenocarcinoma & Squamous cell**
  - Small cell lung cancer
  - Head and neck cancer
  - Gastric and GE junction
- **Mismatch repair deficient tumors (Colon, Cholangiocarcinoma)**
  - Bladder
  - Triple negative breast cancer
  - Ovarian
  - Glioblastoma
  - Hepatocellular carcinoma
  - Mesothelioma
  - Cervical cancer
- **Hodgkin Lymphoma**
  - Diffuse large cell lymphoma
  - Follicular lymphoma
  - T-cell lymphoma (CTCL, PTCL)
- **Merkel Cell**

Minimal to no activity:

- Prostate cancer
- MMR+ Colon cancer
- Myeloma
- Pancreatic Cancer

From NCI review, 10-2015
Are Checkpoint Immunotherapies are “Targeted therapy”?

- Positive PD-L1 staining in NSCLC (proprietary Genentech/Roche PD-L1 IHC)
- High sensitivity and specificity in FFPE samples

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Estimated PD-L1 Prevalence (≈ %)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (SCC)</td>
<td>50%</td>
</tr>
<tr>
<td>NSCLC (adenocarcinoma)</td>
<td>45%</td>
</tr>
<tr>
<td>Colon</td>
<td>45%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>40%</td>
</tr>
<tr>
<td>Renal</td>
<td>20%</td>
</tr>
</tbody>
</table>

Nearly all human tumors include a subset that expresses PD-L1

Intra-tumoral PD-L1 expression and response to PD-1/PD-L1 blockade

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab Solid Tumors</th>
<th>Nivolumab Melanoma</th>
<th>Nivolumab Melanoma</th>
<th>MPD152380A Solid Tumors</th>
<th>MPD152380A Melanoma</th>
<th>Pembrolizumab Melanoma</th>
<th>Pembrolizumab NSCLC</th>
<th>Pembrolizumab NSCLC</th>
<th>Pembrolizumab Head &amp; Neck</th>
<th>Pembrolizumab Bladder</th>
<th>Pembrolizumab Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>42</td>
<td>44</td>
<td>34</td>
<td>94</td>
<td>30</td>
<td>53</td>
<td>113</td>
<td>129</td>
<td>65</td>
<td>55</td>
<td>411</td>
</tr>
<tr>
<td>Response Rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Unselected</td>
<td>21%</td>
<td>32%</td>
<td>29%</td>
<td>22%</td>
<td>23%</td>
<td>23%</td>
<td>40%</td>
<td>19%</td>
<td>26%</td>
<td>18%</td>
<td>40%</td>
</tr>
<tr>
<td>PD-L1 +</td>
<td>36%</td>
<td>67%</td>
<td>44%</td>
<td>39%</td>
<td>27%</td>
<td>46%</td>
<td>49%</td>
<td>37%</td>
<td>43%</td>
<td>46%</td>
<td>49%</td>
</tr>
<tr>
<td>PD-L1 -</td>
<td>0%</td>
<td>19%</td>
<td>17%</td>
<td>13%</td>
<td>20%</td>
<td>15%</td>
<td>13%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td>13%</td>
</tr>
</tbody>
</table>

from Callahan: ASCO 2014
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

Docetaxel
75 mg/m² IV Q3W

Nivolumab
3 mg/kg IV Q2W

Treat until progression or unacceptable toxicity or withdrawal of consent

POSITIVE

Overall Survival (OS)

CheckMate 017: Squamous
CheckMate 057: Non-Squamous

Marker positive Strategy: PD-L1+

Pembrolizumab Phase III Trial
Stage IIIIB/IV NSCLC

Docetaxel
75 mg/m² IV Q3W

Pembro
2 mg/kg IV Q3W

Pembro
10 mg/kg IV Q3W

Treat until progression or unacceptable toxicity or withdrawal of consent

POSITIVE

Overall Survival (OS)

KEYNOTE 010:
Squamous + Non-Squamous
Phase III Trials of Nivolumuab PD-1 Therapy Compared to Docetaxel in 2nd Line Advanced/Metastatic NSCLC

**CheckMate 017: Squamous**

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

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

- Docetaxel
  75 mg/m² IV
  Q3W

- Nivolumab
  3 mg/kg IV
  Q2W

- Treat until progression or unacceptable toxicity or withdrawal of consent

- Overall Survival (OS)

  *Spigal et al: ASCO 2015*

**CheckMate 057: Non-Squamous**

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

- Nivolumab Phase III Trials
  Stage IIIIB/IV Non- Squam (057) NSCLC

- Docetaxel
  75 mg/m² IV
  Q3W

- Nivolumab
  3 mg/kg IV
  Q2W

- Treat until progression or unacceptable toxicity or withdrawal of consent

- Overall Survival (OS)

  *Paz-Ares et al: LBA109 ASCO 2015*
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: 135
- Docetaxel: 137
- mOS (mo): 9.2 (7.3, 13.3) vs. 6.0 (5.1, 7.3)
- # events: 86 vs. 113
- HR = 0.69 (95% CI: 0.44, 0.97); P = 0.00025
- 1-yr OS rate = 42%
- 1-yr OS rate = 24%
- **Kinetics of Survival Curves (OS)**: Early & continuous separation

**Trial 057: Non-Squamous Cell**
- Nivolumab: 292
- Docetaxel: 280
- mOS (mo): 12.2 vs. 9.4
- HR = 0.73 (95% CI: 0.59, 0.99); P = 0.0015
- 1-yr OS rate = 51%
- 1-yr OS rate = 39%
- **Kinetics of Survival Curves (OS)**: Cross-over but subsequent separation
CheckMate 017: Nivolumab vs Docetaxel in Advanced Squamous NSCLC

OS by PD-L1 Expression

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>mOS (mo) Nivolumab</th>
<th>mOS (mo) Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 ≥1%</td>
<td>9.3</td>
<td>7.2</td>
</tr>
<tr>
<td>PD-L1 &lt;1%</td>
<td>8.7</td>
<td>5.9</td>
</tr>
<tr>
<td>PD-L1 ≥5%</td>
<td>10</td>
<td>6.4</td>
</tr>
<tr>
<td>PD-L1 &lt;5%</td>
<td>8.5</td>
<td>6.1</td>
</tr>
<tr>
<td>PD-L1 ≥10%</td>
<td>11</td>
<td>7.1</td>
</tr>
<tr>
<td>PD-L1 &lt;10%</td>
<td>8.2</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Survival benefit of nivolumab was independent of PDL1 expression levels in Squamous lung cancer
CheckMate 057: Nivo vs. Doc in advanced Non-Squamous NSCLC

**OS by PD-L1 Expression**

- **≥1% PD-L1 expression level**
  - Nivo: 17.2 mo
  - Doc: 5.0 mo
  - HR (95% CI) = 0.69 (0.43, 0.82)

- **≥5% PD-L1 expression level**
  - Nivo: 15.2 mo
  - Doc: 8.1 mo
  - HR (95% CI) = 0.43 (0.30, 0.53)

- **≥10% PD-L1 expression level**
  - Nivo: 19.4 mo
  - Doc: 8.0 mo
  - HR (95% CI) = 0.40 (0.26, 0.59)

- **<1% PD-L1 expression level**
  - Nivo: 10.4 mo
  - Doc: 10.1 mo
  - HR (95% CI) = 0.90 (0.66, 1.24)

- **<5% PD-L1 expression level**
  - Nivo: 9.5 mo
  - Doc: 10.1 mo
  - HR (95% CI) = 1.01 (0.77, 1.34)

- **<10% PD-L1 expression level**
  - Nivo: 9.5 mo
  - Doc: 10.3 mo
  - HR (95% CI) = 1.00 (0.78, 1.31)

Symbols represent censored observations.

**OS benefit correlates with PD-L1 expression in this Non-SQ trial.**
Contrasts with trial 017 in SQ.
### OS, PD-L1 TPS ≥50% Stratum

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median (95% CI), mo</th>
<th>Rate at 1 y</th>
<th>HR(^a) (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>14.9 (10.4-NR)</td>
<td>53.4%</td>
<td>0.54 (0.38-0.77)</td>
<td>0.00024</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>17.3 (11.8-NR)</td>
<td>58.1%</td>
<td>0.50 (0.36-0.70)</td>
<td>0.00002</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.2 (6.4-10.7)</td>
<td>38.0%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)Comparison of pembrolizumab vs docetaxel.
Evolution of NSCLC Subtyping from Histologic to a Multitude of Genomically-defined Subsets:
Novel Clinical Trial Designs

Histology-based Subtyping

Li, Gandara et al: JCO 2013 (adapted from Pao et al)
Evolution of NSCLC Subtyping from Histologic to a Multitude of Genomically-defined Subsets: Novel Clinical Trial Designs

Unmet needs addressed by Master Protocols:

- How to develop drugs for uncommon-rare genotypes?
- How to apply broad-based screening (NGS)?
- How to achieve acceptable turn-around times for molecular testing for therapy initiation? (<2 weeks)
- How to expedite the new drug-biomarker FDA approval process? (companion diagnostic)

Li, Mack, Kung, Gandara: JCO 2013
S1400 Master Protocol (Lung-MAP):
A Unique Private-Public Partnership within the NCTN
S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy

Biomarker Profiling (NGS/CLIA)

Multiple Phase II-III Sub-studies with "Rolling Opening & Closure"

Biomarker A

TT A CT*

Primary Endpoint PFS/OS

Biomarker B

TT B CT*

Primary Endpoint PFS/OS

Biomarker C

TT C+CT CT*

Primary Endpoint PFS/OS

Biomarker D

TT D+E E*

Primary Endpoint PFS/OS

Biomarker Non-Match

Non-Match Drug

CT*

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

Each Sub-Study independent of the others.
Each Sub-study designed for registration of a drug-biomarker combination.
Self-sustaining with new Sub-studies in planning stages.
**LUNG-MAP (S1400): Squamous Lung Cancer- 2nd Line Therapy**

**Common Broad Platform**
CLIA Biomarker Profiling

**Non-match**

- **CT**
- **CT**
- **CT**
- **CT**
- **E**

**Archival FFPE tumor, fresh CNB if needed**

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

**PI3K**
M: **PIK3CA mut**
- **GDC-0032**
- **CT**
- **Endpoint PFS/OS**

**CDK4/6**
M: **CCND1, CCND2, CCND3, cdk4 ampl**
- **PD-0332991**
- **CT**
- **Endpoint PFS/OS**

**FGFR**
M: **FGFR ampl, mut, fusion**
- **AZD4547**
- **CT**
- **Endpoint PFS/OS**

**HGF**
M: **c-Met Expr**
- **AMG102+E**
- **E**
- **Endpoint PFS/OS**

**Anti-PD-L1: MEDI4736**

**LUNG-MAP**

*Project Chair: V. Papadimitrakopoulou*
*Steering Committee Chair: R. Herbst*
*SWOG Lung Chair: D. Gandara*
Organizers: NCI-TMSC, FDA, FNIH, FOCR

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 ~65% in matching a patient with a drug/biomarker arm"
Updated Lung-MAP Trial Schema (Expected Fall 2015 with Revs #3 & 4)

Stage 1
- PI3K
- CDK4/6
- FGFR
- HRD

GDC-0032 | Palbociclib | AZD4547 | BMN 673

Stage 2
- GDC-0032 Vs SoC
- Palbociclib Vs Soc
- AZD4547 Vs SoC
- BMN 673 Vs SoC

Checkpoint
- Nivo/Ipi
- Nivolumab
- MEDI4736/Treme
- Vs Docetaxel

Matched Sub-studies
- Naive
- Refractory

Non-match Sub-studies

1 Revision #3: Expected September/October 2015
2 Revision #4: Expected December 2015/January 2016

- Lung-MAP amended to 2nd line therapy and beyond to accommodate Nivolumab approval
- Pre-screening added back
- Eligibility criteria broadened
“Eating an Elephant”: An Analogy to Defeating Lung Cancer

“If you want to eat an elephant, you need a strategy”

“If you try to do it in one bite, you will choke on it”

M. Vestager. – May 25, 2015
EU Antitrust Chief
Danish politician
“Eating an Elephant”: An Analogy to Defeating Lung Cancer

“If you want to eat (defeat) LUNG CANCER, you need a strategy”

“If you try to do it in one bite, you will choke on it”

There is no single solution to defeating Lung Cancer. Like the elephant, it will take many bites.