Medical Treatment of Advanced Lung Cancer

Oncology for Scientists
April 26, 2018
Most Lung Cancers Present in Advanced Stage

Percent of Cases by Stage

- Localized: Confined to primary site
- Regional: Spread to regional lymph nodes
- Distant: Cancer has metastasized
- Unknown: Unstaged

© LUNGevity Foundation
Prognosis according to staging

SCLC

\(Eisen\ et\ al.\ BMC\ Cancer\ 2008\)

NSCLC

\(Goldstraw\ et\ al.\ J\ Thorac\ Oncol\ 2007\)
Pathology for Clinicians

Lung Carcinoma
- 85%
  - Non-small Cell Lung Carcinoma (NSCLC)
    - 30%
      - Squamous Cell
    - 40%
      - Adenocarcinoma
    - 10%
      - Large Cell
- 15%
  - Small Cell Lung Carcinoma (SCLC)
    - Neuroendocrine
      - LCNEC
      - Carcinoid
      - 5%
Molecular Profiling of Lung Cancer

Squamous Cell NSCLC

Adenocarcinoma NSCLC

SCLC

Immune Profiling of Lung Cancer

Lawrence et al. Nature 2012
Systemic Treatment Modalities
Chemotherapy

- **Platinum Analogs (G₁-S)**
  - Cisplatin
  - Carboplatin
- **Topoisomerase II Inhibitors (G₂)**
  - Etoposide
- **Anti-metabolites (S)**
  - Pemetrexed
  - Gemcitabine
- **Microtubule inhibitors (M)**
  - Taxanes
    - Paclitaxel
    - Docetaxel
  - Vinorelbine
Systemic Treatment Modalities
Targeted Therapies

Receptor TKIs

From the RAS initiative, NCI Schubbert et al. Nat Rev Cancer 2007
Systemic Treatment Modalities
Targeted Therapies

• Immune Checkpoint Inhibitors – Releasing the immune “brakes”
Systemic Treatment Modalities

- Chemotherapy
- Genomically targeted therapy
- Combination with genomically targeted agent and immune checkpoint therapy
- Immune checkpoint therapy
Pathology for Clinicians

Lung Carcinoma

Non-small Cell Lung Carcinoma (NSCLC)

- 85%
- 15%

Non-squamous NSCLC

- 40%
- 10%

Squamous Cell

- 30%

Small Cell Lung Carcinoma (SCLC)

- Neuroendocrine
- LCNEC
- Carcinoid
- 5%

Adenocarcinoma

Large Cell
Small Cell Lung Cancer (SCLC)

• Treatment options have not changed much over last 30 years
• Rapid doubling time, initially very sensitive to chemotherapy and radiation
  – 60-70% responsive to platinum-based CHEMOTHERAPY (cisplatin/etoposide)
• Limited options when cancer invariably relapses. Very insensitive to therapy on relapse
Frontline Combination Chemotherapy in ES-SCLC

Median OS ~10mo
1yr survival ~37%

Neill et al. JCO 2005
Second Line Chemotherapy in Relapsed ES-SCLC

Median OS 25.9 weeks
6-mo survival ~49%

O’Brien et al. JCO 2006
TMB-evaluable patients treated with N+I (n=78) in the high vs medium and low TMB cohorts:

- ORR: 46.2% vs 16.0% and 22.2%;
- 1-year PFS: 30.0% vs 8.0% and 6.2%;
- 1-year OS 62.4% vs 19.6% and 23.4%
Immunotherapy in Relapsed ES-SCLC - TMB

CHECKMATE – 032 -TMB-evaluable patients treated with N+I (n=78) in the high vs medium and low TMB cohorts:

ORR: 46.2% vs 16.0% and 22.2%;
1-year PFS: 30.0% vs 8.0% and 6.2%;
1-year OS 62.4% vs 19.6% and 23.4%
Cancer Cell

Chemosensitive Relapse in Small Cell Lung Cancer Proceeds through an EZH2-SLFN11 Axis

Graphical Abstract

Authors
Eric E. Gardner, Benjamin H. Lok, Valentina E. Schneeberger, ..., Pierre P. Massion, Charles M. Rudin, John T. Poirier

Correspondence
rudinc@mskcc.org (C.M.R.), poirierj@mskcc.org (J.T.P.)

In Brief
By generating paired chemonaive and chemoresistant small cell lung cancer (SCLC) patient-derived xenograft models, Gardner et al. find that EZH2 promotes chemo resistance by epigenetically silencing SLFN11. EZH2 inhibition prevents acquisition of chemo resistance and improves chemothrapeutatic efficacy in SCLC.
PDX model of relapsed SCLC

From the RAS initiative, NCI
Gardner et al. Cancer Cell. 2017
Pathology for Clinicians

Lung Carcinoma
- Non-small Cell Lung Carcinoma (NSCLC)
  - Squamous Cell: 30%
  - Non-squamous NSCLC
    - Adenocarcinoma: 40%
    - Large Cell: 10%
  - Small Cell Lung Carcinoma (SCLC)
    - Neuroendocrine
      - LCNEC: 15%
      - Carcinoid: 5%
Frontline Combination Chemotherapy in Stage IV NSCLC

HR 0.73-0.77
10% absolute survival benefit at one year
Frontline Combination Chemotherapy in Stage IV NSCLC
Cisplatin/Pemetrexed increased survival in non-squamous histology compared to Cisplatin/Gemcitabine

Scagliotti et al. JCO 2008
Frontline Combination Chemotherapy in Stage IV NSCLC
Where we were in 2008

Adding **Bevacizumab** to Carbo/Paclitaxel chemotherapy improved Survival
Median OS from 10 months to 12 months
Targeted Therapy/Precision Medicine Era
EGFR TKI in Stage IV NSCLC

Erlotinib + Chemo Inferior first line in unselected patients

Gridelli et al. JCO. 2012
EGFR TKI in Stage IV NSCLC

Gefitinib improved PFS compared to chemo in selected patients with activating EGFR mutations

Maemondo et al. NEJM 2010
EGFR TKI in Stage IV NSCLC with activating EGFR mutations

Soria et al. NEJM 2017
ALK TKI in Stage IV NSCLC with ALK-ROS1 rearrangements

A Progression-free Survival

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.34–0.65)
P<0.001 by log-rank test

No. at Risk
Alectinib 152 135 113 109 97 81 67 35 15 3
Crizotinib 151 132 104 84 65 46 35 16 5
Immunotherapy in Stage IV NSCLC

A percentage (~15-20%) of durable responders to anti-PD-1 therapy

- First report of long-term survival rate in patients with metastatic NSCLC treated with an immune checkpoint inhibitor
- According to the National Cancer Institute's SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%
FDA-approved Checkpoint Inhibitors for use in NSCLC

Nivolumab
PD-1

2008
Nivo FIH trial

2012
Pembro FIH trial

2015 (March)
Nivolumab FDA approved in 2nd line Sq NSCLC

2015 (Fall)
Nivolumumab Approved in Fall for 2nd line Non-sq NSCLC

Pembrolizumab
PD-1

2012
Pembro FIH trial

2015 (Fall)
Pembrolizumab FDA approved 1st line NSCLC (PD-L1 > 50%)
Pembrolizumab FDA approved in 2nd line NSCLC (PDL1 > 1%)

Atezolizumab
PD-L1

2015 (Fall)
Pembrolizumab FDA approved in 2nd line NSCLC (PD-L1 > 50%)

Durvalumab
PD-L1

2016 (Fall)
Pembrolizumab + Pemetrexed and Carboplatin
FDA approved 1st line NSCLC

2017 (May)
Pembrolizumab FDA approved 1st line NSCLC

2017 (July)
Durvalumab FDA Breakthrough Therapy Designation for Stage III NSCLC

Brahmer et al. NEJM 2015
PD1/PD-L1 Inhibitors increase Overall Survival in 2L Advanced NSCLC

CHECKMATE 017 (squamous)

CHECKMATE 057 (non-squamous)

KEYNOTE 010 (TPS ≥ 1%)

OAK

PD1/PD-L1 Staining of NSCLC with increasing levels of expression

**PD-L1 IHC**

- Percentage of neoplastic cells showing membranous staining of PD-L1 proportion score (PS)
- Need > 100 cancer cells in order to calculate PS
Pembrolizumab versus Chemotherapy for PD-L1 IHC High NSCLC

Survival benefit

- Estimated Overall Survival at 12 months: 70% (Pembrolizumab) vs 54% (Chemotherapy)
- Hazard Ratio for death: 0.60
- Significantly longer OS in Pembrolizumab group despite cross-over in 50% of patients in control arm (60% if you count crossover to any PD-1 inhibitor)
- Median OS not reached in either group
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

Chemotherapy plus pembrolizumab in first line metastatic NSCLC

A  Overall Survival

Hazard ratio for death, 0.49 (95% CI, 0.38–0.64)  
P < 0.001

<table>
<thead>
<tr>
<th>Months</th>
<th>Pembrolizumab combination</th>
<th>Placebo combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>410</td>
<td>206</td>
</tr>
<tr>
<td>3</td>
<td>377</td>
<td>183</td>
</tr>
<tr>
<td>6</td>
<td>347</td>
<td>149</td>
</tr>
<tr>
<td>9</td>
<td>278</td>
<td>104</td>
</tr>
<tr>
<td>12</td>
<td>163</td>
<td>59</td>
</tr>
<tr>
<td>15</td>
<td>71</td>
<td>25</td>
</tr>
<tr>
<td>18</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>21</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Gandhi et al. NEJM. 2018
Thank You!

Edwin.Yau@RoswellPark.org