Neoadjuvant Therapy in Lung Cancer

Patrick Forde, M.B. MRCP UK
Director, Thoracic Oncology Clinical Research Program
Associate Professor of Oncology
Bloomberg-Kimmel Institute for Cancer Immunotherapy
Johns Hopkins University

#MelanomaNeoadjuvant
Disclosures

• Advisory Board/Consultant – AstraZeneca, BMS
• Steering Committee for Clinical Trials – AstraZeneca, BMS, Janssen
• Research funding (to institution) – AstraZeneca, BMS, Corvus, Kyowa, Novartis,
• Investigational use of drugs will be discussed in context of ongoing research studies
Cresting Wave
Perioperative IO in Lung Cancer

• Ct.gov search for PD-(L)1 drug names and “surgery”
  – total of 302 actively recruiting perioperative IO trials across tumor types
  – 162/302 involve neoadjuvant anti-PD-(L)1
  – 56 neoadjuvant anti-PD-(L)1 NSCLC trials on clinicaltrials.gov
# Current approach & prognosis for potentially resectable NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Treatment</th>
<th>5 Year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA/B</td>
<td>T1-2N0M0</td>
<td>Sx vs SBRT</td>
<td>77-92%</td>
</tr>
<tr>
<td>Stage IIA/B</td>
<td>T1-2N1M0, T3N0M0</td>
<td>CTx =&gt; Sx, Sx =&gt; CTx</td>
<td>53-60%</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T3N1M0, T4N1-0M0, T1-3N2M0</td>
<td>CRT vs CRT + Sx vs CTx + Sx vs Sx + CTx vs Sx vs CRT??????</td>
<td>36%</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T1-3N3M0, T4N2-3M0</td>
<td>CRT</td>
<td>13-26%</td>
</tr>
</tbody>
</table>
Meta-analysis: Lung Adjuvant Cisplatin Evaluation (LACE)

5 studies since 1995
- BLT, ALPI, IALT, JBR.10, ANITA

Pooled individual data
- 4585 patients

Chemotherapy
- ↓6.9% lung CA death
- ↑1.4% non-CA death

HR 0.89 (95% CI 0.82 – 0.96); p = 0.005
Absolute benefit 5.4% at 5 years

Perioperative therapy in NSCLC

Historic Perspective - Neoadjuvant

<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative chemotherapy*</th>
<th>Control*</th>
<th>O-E</th>
<th>Variance</th>
<th>HR (95% CI); p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>France 1990</td>
<td>8/13</td>
<td>8/13</td>
<td>0.32</td>
<td>3.97</td>
<td></td>
</tr>
<tr>
<td>MD Anderson 1994</td>
<td>19/28</td>
<td>27/32</td>
<td>-6.40</td>
<td>11.19</td>
<td></td>
</tr>
<tr>
<td>Spain 1994</td>
<td>19/29</td>
<td>27/30</td>
<td>-8.88</td>
<td>9.65</td>
<td></td>
</tr>
<tr>
<td>MIP 91</td>
<td>137/179</td>
<td>246/176</td>
<td>-12.99</td>
<td>70.22</td>
<td></td>
</tr>
<tr>
<td>SWOG S9015</td>
<td>3/5</td>
<td>12/16</td>
<td>-1.04</td>
<td>2.94</td>
<td></td>
</tr>
<tr>
<td>JCOG 9209</td>
<td>28/31</td>
<td>25/31</td>
<td>2.25</td>
<td>12.97</td>
<td></td>
</tr>
<tr>
<td>Finland 2003</td>
<td>19/30</td>
<td>19/32</td>
<td>0.50</td>
<td>9.48</td>
<td></td>
</tr>
<tr>
<td>MRC BLT</td>
<td>4/5</td>
<td>3/5</td>
<td>1.26</td>
<td>1.60</td>
<td></td>
</tr>
<tr>
<td>MRC LU22</td>
<td>151/258</td>
<td>158/261</td>
<td>-2.92</td>
<td>77.01</td>
<td></td>
</tr>
<tr>
<td>SWOG S9900</td>
<td>93/180</td>
<td>103/174</td>
<td>-9.31</td>
<td>48.84</td>
<td></td>
</tr>
<tr>
<td>China 2002</td>
<td>26/32</td>
<td>18/23</td>
<td>1.42</td>
<td>10.78</td>
<td></td>
</tr>
<tr>
<td>China 2005</td>
<td>8/19</td>
<td>14/21</td>
<td>-3.31</td>
<td>5.44</td>
<td></td>
</tr>
<tr>
<td>CHEST</td>
<td>45/129</td>
<td>61/141</td>
<td>-10.27</td>
<td>26.39</td>
<td></td>
</tr>
<tr>
<td>NATCH</td>
<td>99/201</td>
<td>109/212</td>
<td>-4.11</td>
<td>51.95</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>682/1178</td>
<td>745/1207</td>
<td>-50.62</td>
<td>351.78</td>
<td></td>
</tr>
</tbody>
</table>

Overall HR

0.87 (0.78-0.96), p=0.007 (fixed effect)
0.86 (0.75-0.98), p=0.03 (random effects)
Heterogeneity: $\chi^2=18.75$, df=14, p=0.18, I²=25%
Drug Development in Lung Cancer

• IO & targeted therapy drug development mandates a new paradigm for resectable NSCLC
  - hundreds of candidate agents in development
  - timeline from phase 1 to 3 has shortened to 2-3 yrs
  → potential read out within 5 years of FIH study

• 2016-2019 - New FDA approved indications in advanced NSCLC

27
Drug Development in Lung Cancer

• IO & targeted therapy drug development mandates a new paradigm for resectable NSCLC
  - hundreds of candidate agents in development
  - timeline from phase 1 to 3 has shortened to 2-3 yrs
  → potential read out within 5 years of FIH study

• 2016-2019 – New FDA approved indications in advanced NSCLC

• 2004-2019 – New systemic therapies for resectable NSCLC
• In United States – approximately 50:50 split between neoadjuvant chemotherapy and chemoradiation for stage IIIA NSCLC

• Growing interest in neoadjuvant IO – educational sessions at all national thoracic surgery meetings in 2019

• Nearly all patients seen first by surgeons
  - incentive to resect + some concerns about progression
Limitations of Adjuvant Therapy Trials
Lung Cancer

• Median time from enrollment of first patient to publication of study results for phase 3 adjuvant NSCLC studies (1990-2016)
  
  11 years

• Absence of significant correlative science that may help enrich for benefit
  - given patient population, toxicity of chemotherapy, and modest benefit to date
• DFS and OS are long term endpoints for early stage lung cancer trials and take years to mature

• Surrogate endpoints such as pathologic complete response (pCR) are used for breast cancer neoadjuvant studies; pCR historically has been rare after neoadjuvant chemo for lung cancer

• Major pathologic response (MPR; ≤10% residual viable tumor cells in the primary) occurs ~20% after neoadjuvant chemotherapy and may predict DFS

<table>
<thead>
<tr>
<th>Percentage of residual viable tumor following neo-adjuvant chemotherapy</th>
<th>Hazard Ratio for death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10%</td>
<td>1.00</td>
</tr>
<tr>
<td>11-30%</td>
<td>2.51 (95% CI 0.91-6.96)</td>
</tr>
<tr>
<td>31-50%</td>
<td>3.39 (95% CI 1.40-8.22)</td>
</tr>
<tr>
<td>51-70%</td>
<td>4.57 (95% CI 1.98-10.52)</td>
</tr>
<tr>
<td>71-100%</td>
<td>4.78 (95% CI 2.06-11.11)</td>
</tr>
</tbody>
</table>
Initial Experience with Neoadjuvant PD-1 Blockade

Longer Term Follow Up

Forde, Chaft, Smith et al. NEJM 2018
Opportunities for interdisciplinary correlative science

- Immune-related pathologic response criteria
  - Cottrell, Taube et al.

- Compartmental analysis of T cell repertoire
  - Zhang, Smith et al.

- Dynamics of ctDNA during neoadjuvant therapy
  - Anagnostou, Forde et al.

- Surgical outcomes after neoadjuvant PD-1 blockade
  - Broderick, Bott et al.
Neoadjuvant PD(L)1 is safe & feasible with encouraging MPR rates

<table>
<thead>
<tr>
<th>Study (phase)</th>
<th>No. Patients</th>
<th>Therapy</th>
<th>No. Cycles</th>
<th>MPR rate</th>
<th>MPR association with RECIST</th>
<th>MPR association with TMB</th>
<th>MPR association with PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>JHH/MSKCC (Ib/II)</td>
<td>22</td>
<td>Nivolumab</td>
<td>2</td>
<td>45% (9/20)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NEOSTAR (II)</td>
<td>44</td>
<td>Nivolumab &amp; Nivo/Ipi</td>
<td>3</td>
<td>19% (4/21)*</td>
<td>Yes</td>
<td>---</td>
<td>Yes</td>
</tr>
<tr>
<td>LCMC3 (II)</td>
<td>101</td>
<td>Atezolizumab</td>
<td>2</td>
<td>19% (15/77)</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

MPR rate: 23.7% (28/118)

MPR with neoadjuvant chemotherapy ~20%
NADIM - Neoadjuvant Chemo-Nivolumab

NSCLC IIIA resectable patients
(N2 or T4N0/N1) → Neoadjuvant treatment
Nivolumab 360 mg + Paclitaxel 200mg/m² + Carboplatin AUC 6 IV, Q3W 3 Cycles → SURGERY
(Surgery in the 3rd or 4th week from day 21 cycle 3 of neoadjuvant treatment)

Blood extraction (C1) → Tumor block
Blood extraction (C3) → Tumor block

Adjuvant treatment
Nivolumab 240mg Q2W for 4 months and Nivolumab 480 mg Q4W for 8 months IV (1 year)

Blood extraction (every 6 months) → FOLLOW UP (3 years)
Pathologic Complete Response of 61% vs. historic control with neoadjuvant chemo of ~5%
Study Design

Population
- Resectable, early-stage (1 [\( \geq 2 \) cm] to IIIA NO-1) NSCLC
- ECOG PS 0 or 1

Randomize

Study treatment: 28-day period
- Arm A: Durvalumab monotherapy
- Arm B: Durvalumab + oleclumab
- Arm C: Durvalumab + monalizumab
- Arm D: Durvalumab + danvatrisen

Initiation additional combination treatment arms
- Arm E: Durvalumab + novel agent TBD
- Arm F: Durvalumab + novel agent TBD

Day 29 to Day 42
- Surgical Resection

Day 105
- Follow-up

Study Period Duration

Dx Screening ≤21 days

RANDOMIZATION

Single Cycle (28 days)

Imaging

up to 21 days post Cycle 1

Surgery

Imaging
Study Design: Predicting Therapeutic Response to Immunotherapy

**Study Design**

**AACR-SU2C**

**Deliverable**: Discover cellular, molecular and imaging features that **distinguish** patients who respond to neoadjuvant nivolumab +/- chemotherapy

**Study Design**

**Neoadjuvant Trial (Forde)**

<table>
<thead>
<tr>
<th>Assays</th>
<th>n=40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bulk RNA-seq (Airway Brushings only)</td>
<td></td>
</tr>
<tr>
<td>Whole Exome Seq (Tumor/Adj. Normal only)</td>
<td></td>
</tr>
<tr>
<td>TCR Seq/MANAFEST</td>
<td></td>
</tr>
<tr>
<td>TEC-seq of ctDNA</td>
<td></td>
</tr>
<tr>
<td>PET Tracer for T-cell activation</td>
<td></td>
</tr>
</tbody>
</table>

**Assays**

- Bronchial & Nasal Brushings
- Images (PET)
- Tumor / Normal
- Blood (Plasma)

**Study Design**

1) Monotherapy (Nivolumab)

**n = 30**

2) Combination Therapy (Nivolumab + ipilimumab)

**n = 10**
Conclusions

- Neoadjuvant IO-based trials
  - accelerate drug development
  - offer crucial insights to guide rationale combination therapy
- Platform studies offer the opportunity to rapidly evaluate pathologic response to novel combinations
- Buy in from multidisciplinary cancer care team is vital
  – surgeons, pulmonary, rad onc, med onc and patient advocates

- Enthusiasm is building in lung cancer community with initial phase 3 results expected in 2020