Neoadjuvant Nivolumab in Early-Stage, Resectable Non-Small Cell Lung Cancers

Abstract 8508

Rationale for Neoadjuvant Nivolumab

- There have been no advances in systemic therapy to treat resectable lung cancers since 2004
- Nivolumab induces deep and durable responses in a subset of patients with lung cancer
- Neoadjuvant nivolumab treatment
  - May induce immunity against micrometastases
  - Allows pathologic response assessment
  - Provides tissue for correlative studies

Neoadjuvant Nivolumab Schema

Newly diagnosed resectable stage I (>2cm)/II/IIIA NSCLC

Tumor Biopsy

PBMC & plasma collection

Nivolumab 3mg/kg IV (Day -14 & Day -28)

Surgical resection (Day 0)

Standard of care postoperative treatment

Tumor & Lymph Node Assessment

TILS

PBMC & plasma collection

Study Endpoints

• **Primary:** Safety & feasibility
  – Drug-related adverse events (90 days post-nivolumab or 30 days post-op, whichever is longer)
  – Feasibility of resection without extended delays (>37 days from preplanned date of surgery)

• **Sample size:**
  – 6 patient safety run-in, then up to total of 20 resected patients

• **Exploratory endpoints**
  – Pathologic response
  – Recurrence free and overall survival
  – Immunologic correlates of clinical outcomes
Patients

22 enrolled

21 treated with preoperative intent

1 withdrawn (diagnosis change to SCLC)

20 resected

1 unresectable (tracheal invasion)

Characteristics  

<table>
<thead>
<tr>
<th></th>
<th>N = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yrs, median (range)</td>
<td>67 (55-84)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>10/11</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>14</td>
</tr>
<tr>
<td>Pleomorphic carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Squamous</td>
<td>6</td>
</tr>
<tr>
<td>Clinical Stage (AJCC 7th ed)</td>
<td></td>
</tr>
<tr>
<td>IA/IB</td>
<td>4</td>
</tr>
<tr>
<td>IIA</td>
<td>5</td>
</tr>
<tr>
<td>IIB</td>
<td>5</td>
</tr>
<tr>
<td>IIIA</td>
<td>7</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>3</td>
</tr>
<tr>
<td>Former/Current</td>
<td>18</td>
</tr>
</tbody>
</table>

Primary Endpoints

- **Feasibility:**
  - Nivolumab did not delay or interfere with surgery in any patients

- **Safety:**
  - One death in the post-operative safety period was unrelated to study drug (sequelae of traumatic fall)

<table>
<thead>
<tr>
<th>Drug-related adverse events</th>
<th>Any grade N(%)</th>
<th>Grade 3-4 N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>1* (5)</td>
<td>0</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia/dysgeusia</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting/diarrhea</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>LFT abnormality</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1* (5)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>CNS (delirium)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Nivo dose #2 was withheld in 1 patient due to fever and pneumonia, surgery was not delayed
Radiographic Responses to 2 Doses of Nivolumab

<table>
<thead>
<tr>
<th>RECIST*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>18 (85%)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

*Measurements per RECIST v1.1 but not confirmed as surgery followed 1st assessment

Major pathologic response (MPR) was seen in 9/21 cases [43% (95% CI 24-63%)].

Pre-treatment PD-L1 positivity [≥1% membranous staining (Dako 28-8)] did not correlate with MPR.

*MPR is defined as ≤10% viable tumor cells\(^1,2\)


Clinical Follow-Up

- Median post-op follow-up is 12 mos (range 2-20)
- None of the patients with MPR have recurred
- 2 of 20 resected patients have recurrent lung cancer
  - 1 solitary brain metastasis, treated now NED x 1 year
  - 1 systemic recurrence 1 year post-op
- 2 deaths
  - Patient who was not resected died of disease
  - 1 death not related to drug or disease

Multiplexed Immunofluorescence Shows Post-Treatment Influx of CD8+ T Cells

Background for Correlative Studies

Mutation Burden and Neoantigen Density Are Associated With Pathologic Response to Neoadjuvant Nivolumab (N = 11)

TCRseq: Deep Sequencing of CDR3 Regions to Analyze the Entire TCR Repertoire and, Thus, T-cell Clonality

~50 V segments

Constant

Rearrangement at the DNA level

N-Region Diversity

CDR3 region generates all the TCR diversity

T Cells Specific for Dominant Mutation-Associated Neoantigen (MANA) Expand in Peripheral Blood Upon Neoadjuvant Treatment With Nivolumab

Activation of 3 T cell clones specific for MANA#7 that are found in tumor

MANA#7-specific T cell clones found in tumor and LN

Frequency of MANA#7 specific T cell clones in peripheral blood over time

Initiate nivolumab

Surgery

Day relative to surgery

Pre-tumor

Normal Lung

Involved LN

Resected tumor

Conclusions

• Nivolumab prior to lung cancer resection did not delay surgery in any of the treated patients
• No unexpected safety signals were seen
• 43% of tumors demonstrated a major pathologic response
• Correlative studies in a subset of tumors:
  — Associated mutation and MANA burden with pathologic response
  — Identified MANA-specific TCRs in blood and tumor
  — Observed temporal increases in MANA-specific TCRs in the peripheral blood after nivolumab treatment, a potential biomarker of nivolumab response