State of Lung Cancer Research
Lung Cancer Research Foundation Scientific Symposium

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Amgen; AstraZeneca; Boehringer Ingelheim; Blueprint; Calithera; Euclises; Genentech; Guardant; Janssen; Lilly; Merck KGA; Precision Health; Seattle Genetics; Takeda; Tesaro

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Outline

• Recent advances
  • Moving targeted therapies and IO into the curative setting
  • Lung cancer screening
  • Growing number of targeted therapies leading to improved survival
  • Immunotherapy improving long term outcomes

• Broader challenges that lung cancer research currently faces and potential changes

• How we can contribute to promote a better future and create a more collaborative scientific environment
20 years of progress on the road less traveled

2020—survival improvements for advanced NSCLC

2018—PD-L1 approval for consolidation post chemoradiation

2011—crizotinib accelerated approval

2004—Adjuvant therapy

2004—identification of EGFR mutations

2000—ECOG 1594

2019—PD-L1 approval for SCLC

2015—PD-1 approval

2004—identification of EGFR mutations
Where we started

19% ORR
8 mo Med Survivor
33% 1 yr survival

Cisplatin/paclitaxel
Cisplatin/gemcitabine
Cisplatin/docetaxel
Carboplatin/paclitaxel

Eternal optimism—hope

**hope**

data: desire accompanied by expectation of or belief in fulfillment

*also*: expectation of fulfillment or success
“…declines accelerated for lung cancer mortality, from 3% annually during 2008 through 2013 to 5% during 2013 through 2017 in men and from 2% to almost 4% in women, spurring the largest ever single-year drop in overall cancer mortality of 2.2% from 2016 to 2017.”
Adjuvant and neoadjuvant chemotherapy improves 5-yr survival in early stage NSCLC

**Post-Op Adjuvant CT**

- Overall Survival (%)
  - Chemotherapy: 48.8%
  - No chemotherapy: 43.5%

**Pre-Op Neoadjuvant CT**

- Survival
  - No preoperative chemotherapy: 45%
  - Preoperative chemotherapy: 40%

Deaths / person years by period:
- Control: 966 / 5,155, 239 / 1,668, 49 / 720
- Chemotherapy: 857 / 5,181, 203 / 1,817, 76 / 790


ADAURA—adjuvant osimertinib improves DFS

Herbst et al ASCO 2020; Wu et al NEJM 2020
# Ongoing Phase III Clinical Trials With Adjuvant Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT</th>
<th>Drug</th>
<th>Stage</th>
<th>Target Accrual</th>
<th>Phase</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEARLS</td>
<td>NCT02504372</td>
<td>S with or without CT → pembrolizumab vs. placebo</td>
<td>IB–IIIA</td>
<td>1080</td>
<td>III</td>
<td>DFS</td>
</tr>
<tr>
<td>BR31</td>
<td>NCT02273375</td>
<td>S with or without CT → durvalumab vs placebo</td>
<td>IB–IIIA</td>
<td>1360</td>
<td>III</td>
<td>DFS, DFS in PD-L1 positive</td>
</tr>
<tr>
<td>ANVIL</td>
<td>NCT02595944</td>
<td>S with or without CT → nivolumab vs. observation</td>
<td>IB–IIIA</td>
<td>903</td>
<td>III</td>
<td>DFS, OS</td>
</tr>
<tr>
<td>ALCHEMIST CHEMO I-O</td>
<td>NCT04267848</td>
<td>S → CT &gt; observation vs CT &gt; pembrolizumab vs. CT + pembrolizumab &gt; pembrolizumab</td>
<td>IB–IIIA</td>
<td>1263</td>
<td>III</td>
<td>DFS, OS</td>
</tr>
<tr>
<td>IMpower010</td>
<td>NCT02486718</td>
<td>S with CT → atezolizumab vs best supportive care</td>
<td>IB–IIIA</td>
<td>1280</td>
<td>III</td>
<td>DFS</td>
</tr>
</tbody>
</table>

CT, adjuvant chemotherapy; DFS, disease-free survival; NCT, National Clinical Trial; OS, overall survival; PD-L1, programmed death-ligand 1; S, surgery.
Mechanisms of enhancing a systemic immune response with neoadjuvant IC inhibitors

**Mechanism 1**
“in situ” expansion of tumor
Specific T cell clones already
In the tumor microenvironment

**Mechanism 2**
Tumor antigen-containing dendritic cells in the tumor traffic to the tumor-draining lymph nodes to enhance production of tumor-specific T cells
### Summary of Results of Trials Using Neoadjuvant Immunotherapy in Patients With Resectable NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>Sample Size</th>
<th>Neoadjuvant Immunotherapy</th>
<th>No. of Cycles</th>
<th>Failure to Surgery After Neoadjuvant, %</th>
<th>Primary End Point</th>
<th>MPR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forde et al. 2018</td>
<td>I–IIIA</td>
<td>22</td>
<td>Nivolumab</td>
<td>2</td>
<td>0</td>
<td>Safety and feasibility</td>
<td>45</td>
</tr>
<tr>
<td>Kwiatkowski et al. 2019</td>
<td>Ib–IIIB</td>
<td>101</td>
<td>Atezolizumab</td>
<td>2</td>
<td>11</td>
<td>MPR</td>
<td>19</td>
</tr>
<tr>
<td>Cascone et al.</td>
<td>I–IIIA</td>
<td>44</td>
<td>Nivolumab vs. nivolumab + ipilimumab</td>
<td>3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11</td>
<td>MPR</td>
<td>17 vs. 33 (ITT)</td>
</tr>
<tr>
<td>Li et al. 2019</td>
<td>IA–IIIB</td>
<td>40</td>
<td>Sintilimab</td>
<td>2</td>
<td>7.5</td>
<td>Safety</td>
<td>40.5</td>
</tr>
<tr>
<td>Shu et al. 2018</td>
<td>IB–IIIA</td>
<td>14</td>
<td>Atezolizumab + carboplatin + nab-paclitaxel</td>
<td>4</td>
<td>21.4</td>
<td>MPR</td>
<td>50</td>
</tr>
<tr>
<td>Provencio et al. 2019</td>
<td>IIIA</td>
<td>46&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Nivolumab + carboplatin + paclitaxel</td>
<td>3</td>
<td>0</td>
<td>PFS at 24 mo</td>
<td>83</td>
</tr>
</tbody>
</table>

ITT, intention-to-treat; MPR, major pathologic response; PFS, progression-free survival.

<sup>a</sup> Three cycles of nivolumab with or without one dose of ipilimumab.

<sup>b</sup> Preliminary data of 41 patients.
# Ongoing Clinical Trials With Neoadjuvant Immune Checkpoint Inhibitors With or Without Chemotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT</th>
<th>Drug</th>
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<th>Target Accrual</th>
<th>Phase</th>
<th>End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>MK3475-223</td>
<td>NCT02938624</td>
<td>Pembrolizumab different dose/regimens → S</td>
<td>I–II</td>
<td>28</td>
<td>I</td>
<td>Toxicity, MPR</td>
</tr>
<tr>
<td>TOP 1501</td>
<td>NCT02818920</td>
<td>Pembrolizumab (200 mg) × 2 cycles → pembrolizumab (200 mg) × 4 cycles</td>
<td>IB–IIIA</td>
<td>32</td>
<td>II</td>
<td>Surgical feasibility</td>
</tr>
<tr>
<td>PRICNEPS</td>
<td>NCT02994576</td>
<td>Atezolizumab (1200 mg) × 1 cycle → S</td>
<td>IB–IIIA (no N2)</td>
<td>60</td>
<td>II</td>
<td>Toxicity</td>
</tr>
<tr>
<td>SAKK 16/14</td>
<td>NCT02572843</td>
<td>CT × 3 → durvalumab (750 mg) × 2 cycles → S → durvalumab (750 mg) × 1 y</td>
<td>IIAA (N2)</td>
<td>68</td>
<td>II</td>
<td>EFS</td>
</tr>
<tr>
<td>IONESCO</td>
<td>NCT03030131</td>
<td>Durvalumab (750 mg) Q2W × 3 cycles → S</td>
<td>IB–II</td>
<td>81</td>
<td>II</td>
<td>R0 resection</td>
</tr>
<tr>
<td>Columbia University</td>
<td>NCT02716038</td>
<td>CT + atezolizumab (1200 mg) × 4 cycles → S</td>
<td>IB–IIIA</td>
<td>30</td>
<td>II</td>
<td>MPR</td>
</tr>
<tr>
<td>KEYNOTE 617</td>
<td>NCT03425643</td>
<td>CT + pembrolizumab (200 mg)/placebo × 4 cycles → S → pembrolizumab/placebo × 13 cycles</td>
<td>II–IIIB (T3-4N2)</td>
<td>786</td>
<td>III</td>
<td>EFS, OS</td>
</tr>
<tr>
<td>CheckMate 816</td>
<td>NCT02998528</td>
<td>CT + nivolumab (360 mg) × 3 cycles → S vs. CT × 3 cycles → S</td>
<td>IB–IIIA</td>
<td>350</td>
<td>III</td>
<td>EFS, pCR</td>
</tr>
<tr>
<td>IMpower 030</td>
<td>NCT03456063</td>
<td>CT + atezolizumab (1200 mg)/placebo × 4 cycles → S → atezolizumab/placebo × 16 cycles</td>
<td>II–IIIB (cT3N2)</td>
<td>374</td>
<td>III</td>
<td>MPR, EFS</td>
</tr>
<tr>
<td>AEGEAN</td>
<td>NCT03800134</td>
<td>CT + durvalumab (1500 mg)/placebo × 3 cycles → S → durvalumab/placebo Q4W × 12 cycles</td>
<td>IIA–IIIB</td>
<td>300</td>
<td>III</td>
<td>MPR</td>
</tr>
</tbody>
</table>

CT, chemotherapy; EFS, event-free survival; MPR, major pathologic response; NCT, National Clinical Trial; OS, overall survival; pCR, pathologic complete response; Q4W, every 4 weeks; S, surgery.

*The third arm of the trial, nivolumab plus ipilimumab, was withdrawn after results from NADIM trial.

Uprety D et al J Thorac Oncol 2020
Analysis of ctDNA for posttreatment surveillance

Chaudhuri AA et al Cancer Discov 2018
4 yr OS update ESMO September 2020
49.6% vs. 36.5%, favoring durvalumab
NLST and NELSON Lung Cancer Incidence and Mortality

**NLST**

**A** Lung Cancer

Cumulative No. of Lung Cancers

Years since Randomization

- Low-dose CT
- Chest radiography

**B** Death from Lung Cancer

Cumulative No. of Lung-Cancer Deaths

Years since Randomization

- Chest radiography
- Low-dose CT

**NELSON**

**A** Lung-Cancer Incidence

Cases per 1000 Person-Yr

Years since Randomization

- Screening group
- Control group

**B** Lung-Cancer Mortality

Deaths per 1000 Person-Yr

Years since Randomization

- Control group
- Screening group


Lung cancer screening misses the mark

Fedewa SA et al. JNCI 2020
<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Mutation prevalence</th>
<th>Therapy</th>
<th>Predicted response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR</strong></td>
<td>Asians 30-40% / Caucasian 10-20%</td>
<td>EGFR TKIs (most mutations) / pan-HER inhibitors</td>
<td>Erlotinib 60-80% Gefitinib 70% Afatinib 60% Dacomitinib 75% Osimertinib 80% / 50-60% (T790M)</td>
</tr>
<tr>
<td><strong>ALK</strong></td>
<td>1-7%</td>
<td>ALK inhibitors / HSP90 inhibitors</td>
<td>Crizotinib 50-60% Ceritinib 60% Alectinib 83% Brigatinib 71% Lorlatinib 76% Ensartinib 75%</td>
</tr>
<tr>
<td><strong>ROS1</strong></td>
<td>1.7%, higher in Asians</td>
<td>ROS1 inhibitors</td>
<td>Crizotinib 60-70%; Ceritinib 60% Lorlatinib 62%; Entrectinib 77%</td>
</tr>
<tr>
<td><strong>NTRK</strong></td>
<td>&lt;1%</td>
<td>NTRK inhibitors</td>
<td>Larotrectinib 76%; Entrectinib 70%</td>
</tr>
<tr>
<td><strong>RET</strong></td>
<td>1.7%, EGFR</td>
<td>RET inhibitors / multitargeted TKI</td>
<td>Selpercatinib 60-80% Pralsetinib 60-70% Cabozantinib 40%; Vandetinib 20%</td>
</tr>
<tr>
<td><strong>BRAF</strong></td>
<td>2%</td>
<td>BRAF/MEK inhibitors</td>
<td>Dabrafenib 30%; Dabraf/trametinib 60%</td>
</tr>
<tr>
<td><strong>MET</strong></td>
<td>4%</td>
<td>MET inhibitors / multitargeted TKI</td>
<td>Capmatinib 60%; Tepotinib / Savolitinib ~50%; Crizotinib 25%</td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td>2%</td>
<td>Trastuzumab; pan-HER inhibitors</td>
<td>Trastuzumab Deruxtecan 60%; Dacomitinib 12%; Ado-trastuzumab 20%; TDM-1 44%</td>
</tr>
<tr>
<td><strong>KRAS G12C</strong></td>
<td>9%</td>
<td>KRAS G12C inhibitors / SHP inhibitors</td>
<td>AMG 510 35%; MRTX 849 45%; LY3499446; JNJ-74699157, others</td>
</tr>
</tbody>
</table>
Timeline of FDA Accelerated Approvals of Small Molecule Tyrosine Kinase Inhibitors Targeting ALK

- **Crizotinib**: Aug 2011
- **Ceritinib**: April 2014
- **Alectinib**: Dec 2015
- **Brigatinib**: April 2017
- **Lorlatinib**: Nov 2018
- **Ensartinib**: ????

Adapted from A Shaw WCLC 2019
Liquid biopsy can facilitate treatment with targeted therapy

41% actionable mutations

11 received treatment

All had PR/SD

Use of cfDNA testing increased detection by 48%
Decrease in incidence-based NSCLC mortality—due to targeted therapy

A Trends in Incidence and Incidence-Based Mortality

B Trends in Lung-Cancer-Specific Survival
FDA First-line Approvals for Immunotherapy in Stage IV NSCLC

8 randomized trials have demonstrated efficacy with ICI + concurrent chemotherapy in the first-line setting in patients without an EGFR- or ALK-positive tumor (KEYNOTE-021G, -189, -407, IMpower130, -131, -132, Checkmate-9LA; IMpower150 allowed EGFR/ALK post-TKI).

3 randomized trials have demonstrated that ICI are appropriate as first-line treatment for selected patients based on tumor PD-L1 expression level and no EGFR- or ALK-driven alteration (KEYNOTE-024, -042 and IMpower110).
Keynote-024—Pembrolizumab frontline overall survival

Brahmer J et al ESMO 2020

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events, n (%</th>
<th>HR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>154</td>
<td>103 (66.9)</td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy b</td>
<td>151</td>
<td>123 (81.6)</td>
<td>(0.48–0.81)</td>
<td></td>
</tr>
</tbody>
</table>
Lung cancer trial enrollment

Ethnic disparities in lung cancer clinical trials leading to FDA oncology drug approvals (vs USA LC population)

Courtesy of Janet Freeman-Daily, The ROS1ders, USA, @JFreemanDaily
Continuing on the road less traveled

The Road Not Taken—Robert Frost
Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;

Then took the other, just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same,

And both that morning equally lay
In leaves, no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

Increased lung cancer cures

Established lung cancer survivorship programs

Improved treatments for SCLC

Enhanced inclusion on clinical trials to meet the needs of all

Lung cancer screening standard per guidelines, and increased access

Artificial intelligence to improve diagnosis

Use of ctDNA to determine recurrence risk

Immunotherapy for early-stage disease

Predictive biomarkers for immunotherapy

Cedars Sinai
Thank you!