Novel Approaches in Non-Small Cell Lung Cancer - Immunotherapy and Others

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Disclosure

• No conflicts of interest
Advanced Studies in Lung Cancer Program for phD
Agenda

- Introduction
- Immunotherapy (IO) for resectable NSCLC
- Update in the treatment of locally advanced NSCLC
- First-line IO for metastatic disease
- Second-line IO
- Immunotherapy in EGFR/ALK-positive patients
- Progression after 1st line IO with or without chemo
- Conclusions
Introduction

➢ Statistics in 2012 identified lung cancer as the most common cancer worldwide contributing 13% of the total number of new cases

➢ Worldwide more than 1 in 10 of all cancers diagnosed in men are lung cancers

➢ Lung cancer is the leading cause of cancer-related deaths worldwide

➢ Properly staging the extent of disease at diagnosis influences the approach to treatment and prognosis

➢ Despite ostensibly curative therapy for stage I–III NSCLC, 30–60% of patients go on to develop metastatic disease

➢ Very heterogeneous disease

Howlader N et al, SEER Cancer Statistics Review (CSR) 2017
Lung Cancer Statistics

The lung cancer epidemic - men
## Lung Cancer Mortality

### Estimated Deaths

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>83,550</td>
<td>70,500</td>
</tr>
<tr>
<td>Prostate</td>
<td>29,430</td>
<td>40,920</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>27,390</td>
<td>23,240</td>
</tr>
<tr>
<td>Pancreas</td>
<td>23,020</td>
<td>21,310</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>20,540</td>
<td>14,070</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,270</td>
<td>11,350</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,850</td>
<td>10,100</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,520</td>
<td>9,660</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,510</td>
<td>8,400</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>10,010</td>
<td>7,340</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>323,630</strong></td>
<td><strong>286,010</strong></td>
</tr>
</tbody>
</table>

Ten Leading Cancer Types for the Estimated New Cancer Deaths by Sex, United States, 2018
Stage at Diagnosis

- Localized (16%)
  - Confined to Primary Site
- Regional (22%)
  - Spread to Regional Lymph Nodes
- Distant (57%)
  - Cancer Has Metastasized
- Unknown (5%)
  - Unstaged

Adapted from SEER 18 2007-2013
Late diagnosis

Care in the Emergency Department UK (BLF 2015)

“The fact that 34% of lung cancer patients* are diagnosed as a result of an emergency presentation may come as a surprise to many doctors working in Emergency Departments (ED).”

Molecular classification starts with histology
Why do we care about the molecular classification?
Lung Cancers and Their Molecular Drivers

**Histologies**
- Adenocarcinoma: 40%
- Large cell carcinoma: 15%
- Squamous cell carcinoma: 25%
- Small cell lung cancer: 15%
- Other: 5%

**Adenocarcinoma**
- Other/wild-type: 21%
- KRAS: 26%
- EGFR: 16%
- HER2: 2%
- RET: 1%
- NTRK1: 2%
- ROS1: 2%
- RIT1: 2%
- DDR2: 3%
- NRG1: 3%
- ALK*: 4%
- MET: 4%
- BRAF: 7%
- NF1: 8%

**Squamous**
- Other/wild-type: 55%
- FGFR1*: 20%
- PK3CA: 12%
- PTEN: 10%
- DDR2: 3%

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American Cancer Society website, [https://goo.gl/p2OzY](https://goo.gl/p2OzY).

*Includes both gene amplifications (*) and mutations.
The issue is the Tissue!

- A surgical specimen is available in ~25% of the patients.
- Bronchial biopsy samples are available in ~50% of the cases, and usually contain low percentage of tumor cells.
- ~25% of the patients are diagnosed on cytology samples.

Coghlin CL et al, JTO 2010, 5:448-452
From tissue to molecular signaling

Outline

1. Lung cancer basics
2. Molecular classification
3. Precision medicine

Hannavan and Weinber, Cell 2000
Multidisciplinary team approach to care is necessary to make the best and most informed decision for the patient.
Milestones in targeted therapy for NSCLC

J. Rotow and T.G. Bivona, Nature Reviews Cancer. 2017
Surgery

type of resection depends on local invasion (T factor)

wedge resection

segmentectomy

lobectomy

pneumonectomy

along with systematic en-bloc dissection of mediastinal lymph node stations!
Neoadjuvant Immunotherapy for resectable disease

Neoadjuvant PD-1 Blockade in Resectable Lung Cancer


ABSTRACT

Key patient inclusion criteria
• Newly diagnosed NSCLC
• Stage I (>2 cm), II, IIIA
• Resectable
  (n=22)

21 pts were evaluable

Primary endpoint(s)
• Safety, feasibility of resection without extended delays

Secondary endpoint
• Objective pathological response criteria

Nivolumab
3 mg/kg IV D14, 28
Resection D0
SOC
✓ Neoadjuvant nivolumab well tolerated and did not delay surgery.
✓ SD (18/21, 85%), PR- 2 (10%), PD 1 (5%)
✓ A major pathological response (<10% viable tumour cells in resection specimen) was achieved in 9/20 (45%) completely resected patients (independently of PD-L1 expression)
Locally advanced NSCLC

Stage III NSCLC
> heterogeneous disease in TNM and resectability

Potentially resectable
- Some IIIA-N2
- Some T4-N0/1

Unresectable
- Bulky IIIA-N2
- N3

Stage III

"Surgical multimodality"

"Non-surgical multimodality"
- Systemic therapy
- Radiotherapy
RTOG 06-17 Trial

- On the basis of encouraging phase II trials, the second aim of this phase III study was to show if addition cetuximab to concurrent standard chemo-therapy improved survival.

**Stratification**
- NSCLC
- Stage IIIA/B
- PS 0–1

- **NSCLC**
- **Stage IIIA/B**
- **PS 0–1**

**R**

- Concurrent CT-RT *
  - RT : 60 Gy (6 weeks)
  - Consolidation CT**

- Concurrent CT-RT *
  - RT : 74 Gy (7 weeks)
  - Consolidation CT**

- Concurrent CT-RT *
  - RT : 60 Gy (6 weeks)
  - Consolidation CT**

- Concurrent CT-RT *
  - RT : 74 Gy (7 weeks)
  - Consolidation CT**

*CT-RT
Carboplatin AUC=2 + paclitaxel 45 mg/m²/week, (6 à 7 weeks)
Cetuximab 400 mg/m² initial dose then 250 mg/m²/week.

**Consolidation CT
Carboplatin AUC=6 + paclitaxel 200 mg/m² (2 cycles)
Cetuximab 250 mg/m²/week

RTOG 06-17 Trial

- Addition of cetuximab to concurrent CT-RT and consolidation treatment provided no benefit survival in stage III unresectable NSCLC.
Rationale for Immunotherapy After CRT

- SoC for locally advanced disease is inadequate
- Potential for neoantigen production with CRT
- Neoantigens are recognized as foreign leading to T-cell infiltration
- ... but the T cells are unable to eradicate the tumor because of checkpoint proteins that interfere with cytotoxic T-cell response (eg, PD-1/PD-L1)
- Checkpoint inhibitors allow the immune system to attack cancer cells

PACIFIC trial: Study design

- Phase III, randomized, double-blind, placebo-controlled, multicenter, global study (26 countries)

**Patients with locally advanced unresectable NSCLC (stage III) in a consolidation setting (n = 702)**

- Absence of progression following at least 2 cycles of platinum-based chemotherapy concomitant with radiation therapy

- **Primary endpoints**
  - PFS, OS

- **Secondary endpoints**
  - ORR, DoR, DSR
  - Safety/tolerability
  - PK, immunogenicity, QoL

Arm 1 (n = 468):
- **Durvalumab** iv. 10 mg/kg q2w for up to 12 months

Arm 2 (n = 234):
- **Placebo** iv. q2w
Results: PFS

PFS was significantly longer with durvalumab than with placebo (Median PFS: 16.8 mo with durvalumab and 5.6 mo with placebo)

**PACIFIC Trial**

**Subgroup Analysis of Prognostic Factors for PFS**

### PFS Subgroup Analysis in the ITT Population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Durvalumab</th>
<th>Placebo</th>
<th>Unstratified Hazard Ratio for Disease Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>476</td>
<td>237</td>
<td>0.55 (0.45–0.68)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>334</td>
<td>166</td>
<td>0.56 (0.44–0.71)</td>
</tr>
<tr>
<td>Female</td>
<td>142</td>
<td>71</td>
<td>0.54 (0.37–0.79)</td>
</tr>
<tr>
<td>Age at randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>261</td>
<td>130</td>
<td>0.43 (0.32–0.57)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>215</td>
<td>107</td>
<td>0.74 (0.54–1.01)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>433</td>
<td>216</td>
<td>0.59 (0.47–0.73)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>43</td>
<td>21</td>
<td>0.29 (0.15–0.57)</td>
</tr>
<tr>
<td>NSCLC disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>252</td>
<td>125</td>
<td>0.53 (0.40–0.71)</td>
</tr>
<tr>
<td>IIIB</td>
<td>212</td>
<td>107</td>
<td>0.59 (0.44–0.80)</td>
</tr>
<tr>
<td>Tumor histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>224</td>
<td>102</td>
<td>0.68 (0.50–0.92)</td>
</tr>
<tr>
<td>Non-squamous</td>
<td>252</td>
<td>135</td>
<td>0.45 (0.33–0.59)</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>9</td>
<td>7</td>
<td>0.55 (0.41–0.75)</td>
</tr>
<tr>
<td>Partial response</td>
<td>232</td>
<td>111</td>
<td>0.55 (0.41–0.74)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>222</td>
<td>114</td>
<td>0.55 (0.41–0.74)</td>
</tr>
<tr>
<td>PD-L1 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25%</td>
<td>115</td>
<td>44</td>
<td>0.41 (0.26–0.65)</td>
</tr>
<tr>
<td>&lt;25%</td>
<td>187</td>
<td>105</td>
<td>0.59 (0.43–0.82)</td>
</tr>
<tr>
<td>Unknown</td>
<td>174</td>
<td>88</td>
<td>0.59 (0.43–0.82)</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>29</td>
<td>14</td>
<td>0.76 (0.35–1.64)</td>
</tr>
<tr>
<td>Negative</td>
<td>315</td>
<td>165</td>
<td>0.47 (0.16–0.60)</td>
</tr>
<tr>
<td>Unknown</td>
<td>132</td>
<td>58</td>
<td>0.79 (0.52–1.20)</td>
</tr>
</tbody>
</table>


**PFS benefit with durvalumab was consistently observed across all subgroups, including nonsmokers, and irrespective of PD-L1 expression before CRT**

PACIFIC Trial
Rationale for Performing Scan Immediately After CRT

PFS* Subgroup Analysis of Additional Factors in the ITT Population

<table>
<thead>
<tr>
<th>Table Description</th>
<th>Durvalumab No. of patients</th>
<th>Placebo No. of patients</th>
<th>Unstratified hazard ratio† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of chemotherapy gemcitabine-based</td>
<td>9</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Type of chemotherapy non-gemcitabine-based</td>
<td>467</td>
<td>232</td>
<td>0.55 (0.45–0.68)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>266</td>
<td>129</td>
<td>0.51 (0.39–0.68)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>199</td>
<td>102</td>
<td>0.61 (0.44–0.83)</td>
</tr>
<tr>
<td>Cisplatin and carboplatin</td>
<td>8</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Last radiation to randomization &lt; 14 days</td>
<td>120</td>
<td>62</td>
<td>0.39 (0.26–0.58)</td>
</tr>
<tr>
<td>Last radiation to randomization ≥ 14 days</td>
<td>356</td>
<td>175</td>
<td>0.63 (0.49–0.80)</td>
</tr>
<tr>
<td>Normal WHO performance status</td>
<td>234</td>
<td>114</td>
<td>0.56 (0.41–0.75)</td>
</tr>
<tr>
<td>Restricted WHO performance status</td>
<td>242</td>
<td>123</td>
<td>0.53 (0.40–0.71)</td>
</tr>
<tr>
<td>Asia</td>
<td>109</td>
<td>68</td>
<td>0.51 (0.34–0.77)</td>
</tr>
<tr>
<td>Europe</td>
<td>217</td>
<td>102</td>
<td>0.62 (0.46–0.84)</td>
</tr>
<tr>
<td>North America and South America</td>
<td>150</td>
<td>67</td>
<td>0.49 (0.33–0.73)</td>
</tr>
<tr>
<td>White</td>
<td>337</td>
<td>157</td>
<td>0.58 (0.45–0.75)</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>12</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Asian</td>
<td>120</td>
<td>72</td>
<td>0.48 (0.32–0.72)</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>6</td>
<td>–</td>
</tr>
</tbody>
</table>

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Subgroup analysis indicates that patients treated with durvalumab sooner (last radiation to randomization < 14 d) had a much better HR for improvement in PFS

*Defined by RECIST v1.1.
†Hazard ratio and 95% CI is not calculated if the subgroup level has less than 20 events.
## PACIFIC Trial

### Metastases in the ITT Population

#### Incidence of New Lesions in the ITT Population*

<table>
<thead>
<tr>
<th>New lesion site</th>
<th>Durvalumab (N=476)</th>
<th>Placebo (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
</tr>
<tr>
<td>Any new lesion</td>
<td>97 (20.4)</td>
<td>76 (32.1)</td>
</tr>
<tr>
<td>Lung</td>
<td>56 (11.8)</td>
<td>41 (17.3)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>27 (5.7)</td>
<td>27 (11.4)</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td><strong>26 (5.5)</strong></td>
<td><strong>26 (11.0)</strong></td>
</tr>
<tr>
<td>Liver</td>
<td>9 (1.9)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Bone</td>
<td>8 (1.7)</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>3 (0.6)</td>
<td>5 (2.1)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (1.9)</td>
<td>5 (2.1)</td>
</tr>
</tbody>
</table>

*According to RECIST v1.1.

†A patient may have had more than one new lesion site.

BICR, Blinded Independent Central Review; RECIST, Response Evaluation Criteria In Solid Tumors.


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Patients treated with durvalumab had a lower rate of metastases, including to the brain.

*According to RECIST v1.1.

†A patient may have had more than one new lesion site.

### PACIFIC Trial

**Safety Profile**

### Adverse Events of any Cause

<table>
<thead>
<tr>
<th>Event</th>
<th>Durvalumab (N=475)</th>
<th>Placebo (N=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade¹</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>Any event</td>
<td>460 (96.8)</td>
<td>142 (29.9)</td>
</tr>
<tr>
<td>Cough</td>
<td>168 (35.4)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Pneumonitis or radiation pneumonitis</td>
<td>161 (33.9)</td>
<td>16 (3.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>113 (23.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>106 (22.3)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>87 (18.3)</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>70 (14.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>68 (14.3)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>66 (13.9)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>62 (13.1)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>59 (12.4)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>58 (12.2)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>58 (12.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>58 (12.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>56 (11.8)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>55 (11.6)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>52 (10.9)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>51 (10.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>50 (10.5)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>39 (8.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>36 (7.6)</td>
<td>14 (2.9)</td>
</tr>
</tbody>
</table>

- **Pneumonitis rate was not as expected[a]**
  - Not very frequent
  - No difference between durvalumab and placebo arms
- **Durvalumab is very well tolerated in general[a]**
- **QoL was not worsened with the addition of durvalumab[b]**

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*Events reported in at least 10% of either group.

*Pneumonitis is a grouped term and was assessed by investigators with subsequent review and adjudication by the study sponsor.

Metastatic Disease
Targeted agents in NSCLC

**NSCLC: frequency of mutations and availability of targeted agents**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Frequency in NSCLC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1</td>
<td>Mutation</td>
<td>1</td>
</tr>
<tr>
<td>ALK</td>
<td>Rearrangement</td>
<td>3–7</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>1–3</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>~4</td>
</tr>
<tr>
<td>EGFR</td>
<td>Mutation</td>
<td>10–35</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>20</td>
</tr>
<tr>
<td>HER2</td>
<td>Mutation</td>
<td>2–4</td>
</tr>
<tr>
<td>KRAS</td>
<td>Mutation</td>
<td>15–25</td>
</tr>
<tr>
<td>MEK1</td>
<td>Mutation</td>
<td>1</td>
</tr>
<tr>
<td>MET</td>
<td>Amplification</td>
<td>2–4</td>
</tr>
<tr>
<td>NRAS</td>
<td>Mutation</td>
<td>1</td>
</tr>
<tr>
<td>NTRK</td>
<td>Rearrangement</td>
<td>1</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>1–3</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation</td>
<td>4–8</td>
</tr>
<tr>
<td>RET</td>
<td>Rearrangement</td>
<td>1</td>
</tr>
<tr>
<td>ROS1</td>
<td>Rearrangement</td>
<td>1</td>
</tr>
</tbody>
</table>

**Key**
- Drugs approved in NSCLC
- Drugs approved in NSCLC, but for other molecular subtype
- Drugs approved in other cancer
- Drugs in clinical development

http://www.mycancergenome.org/content/disease/lung-cancer.
Targeted Therapy

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs

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JAMA2014; 311(19)
TKIs in EGFR-mutated NSCLC

Ferrara et al, JTO, 2017
PFS with 1st and next-generation ALK-TKIs

* After 2 or 3 ALK TKIs, after only crizotinib PFS: NR (12.5; NR)
Facts: death rates falling

- Death rates due to cancer fell by only 8% between 1950 and 2012.
- By 67% in the case of heart disease
- By 77% for cerebrovascular diseases
- By 66% for pneumonia and influenza.

Filipovich A. Cancer World 2017
Immunotherapy
Immunity against cancer

Theory of immune surveillance in tumor immunology

The immune system recognizes tumor Ag as “foreign” and rejects emerging cancer cells continuously.

“Cancer develops if an Imbalance between host immune response and the tumor environment occurs”
Br. Med. J. 1957

Macfarlane Burnet
The vertebrate immune system
Innate and Adaptive immune systems

**Innate**
- Dendritic cell
- Macrophage
- Monocyte
- Mast cell
- Eosinophil
- Basophil
- Neutrophil

**Adaptive**
- B-cell
- CD4+ T-cell
- CD8+ T-cell
- NK cell
- γδ T-cell

**Rapid (hours)**
- Non-specific
- No memory

**Slow (days)**
- Specific
- Memory
T-cells are essential to immunological control of cancer
T-cell activation requires 1+3 signals

T cell activation requires 1+3 signals:
Signal 0 - Disturbance
Timeline of cancer immunotherapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Anti-CTLA-4</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Anti-PD-1</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>Bispecific anti-CD3/CD19</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Anti-PD-1</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Anti-PD-L1</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Anti-PD-L1</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>Autologous DCs producing PAP and GM-CSF</td>
</tr>
<tr>
<td>T-vec</td>
<td>Talimogene laherparepvec, oncolytic attenuated and engineered HSV-1 (GM-CSF)</td>
</tr>
<tr>
<td>CAR-T</td>
<td>Genetically engineered autologous T cells</td>
</tr>
</tbody>
</table>

- Generation 1: 2010-2011
  - Ipilimumab (Bristol-Myers Squibb)
  - Sipuleucel-T (Dendreon, now Valeant Pharmaceuticals)

- Generation 2: 2013-2014
  - Pembrolizumab (Merck)
  - Blinatumomab (Amgen)
  - T-vec (Amgen)
  - CAR-Ts (Novartis)

- Generation 3: 2015-2019
  - Atezolizumab (Genentech/Roche)
  - Durvalumab (AstraZeneca)
  - Multiple therapies under development
Figure 1. Mechanisms of action of cytotoxic T-lymphocyte associated protein 4 (CTLA4) (A) and programmed cell death 1 (PD-1)/programmed death ligand 1 (PD-L1) (B) inhibitors in different phases of the anticancer immune response. MHC, major histocompatibility complex; Ag, antigen; mAb, monoclonal antibody; TCR, T-cell receptor; PD-L2, programmed death ligand 2.
Update in the treatment of lung cancer

'End of an Era' for Chemo in Non-Small Cell Lung Cancer?
KEYNOTE-024: Study Design

- Randomized, open-label phase III trial
  - Stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), enrollment region

Pts with untreated stage IV NSCLC, PD-L1 TPS ≥ 50%, ECOG PS 0/1, no activating EGFR mutation/ALK translocation, no active autoimmune disease needing systemic treatment, no untreated brain metastases (N = 305)

- Pembrolizumab
  - 200 mg IV Q3W for up to 2 yrs (n = 154)

- Platinum-Doublet CT*
  - for 4-6 cycles (n = 151)

  Until PD or unacceptable toxicity

Until PD; crossover allowed to pembrolizumab for up to 2 yrs after BICR-confirmed PD and safety criteria met

- Primary analysis endpoints (median f/u: 11.2 mos)
  - Primary: PFS per RECIST v1.1 (BICR)
  - Secondary: OS, ORR, safety

*Investigator’s choice of: pem + carb; pem + cis; pac + carb; gem + carb; gem + cis. Pem-containing regimens only for nonsquamous histology; these pts could receive pem maintenance treatment.
**KEYNOTE-024: PFS and OS**

**KEYNOTE-024: PFS2**

- **Median PFS2**
  - Pembrolizumab (n = 154): 18.3 mos (95% CI: 12.7-NE)
  - Chemotherapy (n = 151): 8.4 mos (6.8-9.8)
- **HR (95% CI)**
  - Pembrolizumab vs Chemotherapy: 0.54 (0.40-0.72); P < .001

**KEYNOTE-024: OS**

- **Median OS**
  - Pembrolizumab (n = 154): NR (19.4-NE)
  - Chemotherapy (n = 151): 14.5 mos (9.8-19.6)
- **HR (95% CI)**
  - Pembrolizumab vs Chemotherapy: 0.63 (0.46-0.88); P = .003

Conclusions

- Investigators concluded that first-line pembrolizumab should be standard of care for NSCLC pts with tumors having PD-L1 TPS ≥ 50% due to prolonged survival and improved safety profile vs platinum-doublet chemotherapy.
KEYNOTE-042: First-line Pembrolizumab vs Platinum-Based Chemotherapy for Advanced or Metastatic NSCLC With PD-L1 TPS ≥ 1%

CCO Independent Conference Highlights*
of the 2018 ASCO Annual Meeting; June 1-5, 2018; Chicago, Illinois

*CCO is an independent medical education company that provides state-of-the-art medical information to healthcare professionals through conference coverage and other educational programs.

This activity is supported by educational grants from Amgen; Astellas; AstraZeneca; Celgene Corporation; Eisai; Genentech; Janssen; Merck & Co., Inc.; and Seattle Genetics.
First-line Pembrolizumab vs CT in Advanced NSCLC With PD-L1 ≥ 1% (KEYNOTE-042): Background

- Pembrolizumab is a SoC option for both untreated and previously untreated advanced or metastatic NSCLC\(^1\)
  - KEYNOTE-010: pembrolizumab monotherapy significantly improved OS vs docetaxel in advanced NSCLC patients with PD-L1 TPS ≥ 1% who progressed on platinum-containing CT\(^2\)
  - KEYNOTE-024: pembrolizumab monotherapy significantly improved PFS and OS, as well as had a better safety profile, vs platinum-based CT in previously untreated metastatic NSCLC with no sensitizing \textit{EGFR}/\textit{ALK} alterations and with PD-L1 TPS ≥ 50%\(^3\)
  - KEYNOTE-189 and KEYNOTE-407: pembrolizumab combined with CT significantly improved survival outcomes vs CT alone in previously untreated metastatic NSCLC (nonsquamous and squamous, respectively) regardless of PD-L1 expression\(^4,5\)

- Current planned interim analysis of KEYNOTE-042 trial evaluated efficacy, safety of first-line pembrolizumab monotherapy vs platinum-based CT in patients with NSCLC and PD-L1 TPS ≥ 1%\(^6\)
KEYNOTE-042: Study Design

- Randomized, open-label phase III trial
  - Current second interim analysis at 38.3 mos after first patient enrolled; data cutoff: February 26, 2018

Stratified by region (East Asia vs rest of world), ECOG PS (0 vs 1), histology (squamous vs nonsquamous), PD-L1 TPS (≥ 50% vs 1% to 49%)

Patients with untreated locally advanced or metastatic NSCLC, PD-L1 TPS ≥ 1%, no EGFR or ALK alterations, ECOG PS 0/1, no unstable or untreated CNS metastases, no prior pneumonitis requiring systemic corticosteroids (N = 1274)

Pembrolizumab 200 mg Q3W for up to 35 cycles (n = 637*)

Platinum-based CT† for up to 6 cycles (n = 637§)

*PD-L1 22C3 pharmDx IHC assay. †n = 636 treated. ‡Carboplatin AUC 5 or 6 Q3W + either paclitaxel 200 mg/m² Q3W or pemetrexed 500 mg/m² Q3W. Pemetrexed maintenance therapy permitted and highly encouraged for patients with nonsquamous histology (52.3% received). §n = 615 treated.

- Primary endpoints: OS in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1% (overall) populations
  - Study has 91% power with 1-sided α = 0.025 to demonstrate piecewise HR of 0.92 (pre-Mo 6) and 0.73 (post-Mo 6) with 900 deaths/1240 patients in PD-L1 TPS ≥ 1% population

- Secondary endpoints: PFS, ORR (per RECIST v1.1) in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1% (overall) populations; safety in PD-L1 TPS ≥ 1% (overall) population


Slide credit: clinicaloptions.com
KEYNOTE-042: OS in PD-L1 TPS ≥ 1% Population (Primary Endpoint)

Overall Survival

HR: 0.81 (95% CI: 0.71-0.93; P = .0018)

<table>
<thead>
<tr>
<th></th>
<th>Events, n (%)</th>
<th>Median OS, Mos (95% CI)</th>
<th>24-Mo OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>371 (58.2)</td>
<td>16.7 (13.9-19.7)</td>
<td>39.3</td>
</tr>
<tr>
<td>CT</td>
<td>438 (68.8)</td>
<td>12.1 (11.3-13.3)</td>
<td>28.0</td>
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</table>

Patients at risk, n

<table>
<thead>
<tr>
<th>Mos</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
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<tbody>
<tr>
<td></td>
<td>637</td>
<td>463</td>
<td>365</td>
<td>214</td>
<td>112</td>
<td>35</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Overall Survival

KEYNOTE-042: OS in PD-L1 TPS ≥ 50% and ≥ 20% Populations (Primary Endpoint)

**PD-L1 TPS ≥ 50%**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>Median OS, Mos (95% CI)</th>
<th>24-Mo OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>157 (52.5)</td>
<td>20.0 (15.4-24.9)</td>
<td>44.7</td>
</tr>
<tr>
<td>CT</td>
<td>199 (66.3)</td>
<td>12.2 (10.4-14.2)</td>
<td>30.1</td>
</tr>
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</table>

**PD-L1 TPS ≥ 20%**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>Median OS, Mos (95% CI)</th>
<th>24-Mo OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>230 (55.7)</td>
<td>17.7 (15.3-22.1)</td>
<td>40.5</td>
</tr>
<tr>
<td>CT</td>
<td>266 (65.7)</td>
<td>13.0 (11.6-15.3)</td>
<td>29.6</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
KEYNOTE-042: OS in Subgroups of PD-L1 TPS >1% Population

### Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>809/1274</td>
<td>0.81 (0.71-0.93)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 yr</td>
<td>444/707</td>
<td>0.81 (0.67-0.98)</td>
</tr>
<tr>
<td>≥ 65 yr</td>
<td>365/567</td>
<td>0.82 (0.66-1.01)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>584/902</td>
<td>0.80 (0.68-0.94)</td>
</tr>
<tr>
<td>Female</td>
<td>225/372</td>
<td>0.89 (0.68-1.17)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>215/390</td>
<td>0.77 (0.59-1.01)</td>
</tr>
<tr>
<td>1</td>
<td>594/884</td>
<td>0.83 (0.71-0.98)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Asia</td>
<td>196/370</td>
<td>0.79 (0.59-1.05)</td>
</tr>
<tr>
<td>Rest of world</td>
<td>613/904</td>
<td>0.82 (0.70-0.96)</td>
</tr>
</tbody>
</table>

### Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/Patients</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>343/492</td>
<td>0.75 (0.60-0.93)</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>466/782</td>
<td>0.86 (0.72-1.03)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>164/282</td>
<td>1.00 (0.73-1.37)</td>
</tr>
<tr>
<td>Former</td>
<td>471/721</td>
<td>0.71 (0.59-0.86)</td>
</tr>
<tr>
<td>Current</td>
<td>175/271</td>
<td>0.95 (0.70-1.29)</td>
</tr>
<tr>
<td>CT regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pem + Carbo</td>
<td>371/636</td>
<td>0.87 (0.71-1.07)</td>
</tr>
<tr>
<td>Pac + Carbo</td>
<td>438/638</td>
<td>0.74 (0.61-0.90)</td>
</tr>
<tr>
<td>Disease status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>711/1114</td>
<td>0.83 (0.71-0.96)</td>
</tr>
<tr>
<td>Locally adv</td>
<td>98/160</td>
<td>0.74 (0.49-1.13)</td>
</tr>
</tbody>
</table>

Dotted vertical line represents the HR in the total population.

KEYNOTE-042: Safety in All Treated Patients

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Pembrolizumab (n = 636)</th>
<th>CT (n = 615)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. doses (range)</td>
<td>9 (1-36)</td>
<td>6 (1-42)</td>
</tr>
<tr>
<td>Treatment-related AEs, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Grade 3-5</td>
<td>113 (17.8)</td>
<td>252 (41.0)</td>
</tr>
<tr>
<td>▪ Leading to death</td>
<td>13 (2.0)</td>
<td>14 (2.3)</td>
</tr>
<tr>
<td>▪ Leading to discontinuation</td>
<td>57 (9.0)</td>
<td>58 (9.4)</td>
</tr>
<tr>
<td>Immune-mediated AEs and infusion reactions, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Grade 3-5</td>
<td>51 (8.0)</td>
<td>9 (1.5)</td>
</tr>
<tr>
<td>▪ Leading to death</td>
<td>1 (0.2)*</td>
<td>0</td>
</tr>
</tbody>
</table>

*Pneumonitis.*
KEYNOTE-042: Conclusions

- In patients with advanced or metastatic NSCLC without EGFR/ALK alterations and with PD-L1 TPS ≥ 1%, first-line pembrolizumab significantly improved OS vs platinum-based CT
  - HR: 0.81 (95% CI: 0.71-0.93; P = .0018)

- Greater benefit of pembrolizumab monotherapy with higher levels of PD-L1 expression consistent with prior reports in this setting
  - TPS ≥ 50%, HR: 0.69 (95% CI: 0.56-0.85; P = .0003)
  - TPS ≥ 20%, HR: 0.77 (95% CI: 0.64-0.92; P = .0020)

- Analysis found no significant improvement in PFS with pembrolizumab, with study continuing to evaluate

- Responses more durable with pembrolizumab vs CT at all levels of PD-L1 expression

- TRAEs consistent with known safety profiles, less frequent with pembrolizumab despite longer exposure

- Investigators concluded that data support expanded use of pembrolizumab monotherapy as a standard first-line treatment option for all PD-L1-positive cancers
Immunotherapy+anti-VEGFR+ChT

IMpower150: Study Design

- Multicenter, open-label, randomized phase III trial (data cutoff: January 22, 2018)
  - Stratified by sex, PD-L1 expression, liver metastases
  - Patients with stage IV or recurrent metastatic nonsquamous NSCLC, no prior CT,* and tumor tissue available for biomarker analysis (N = 1202)

- Atezolizumab 1200 mg IV Q3W + Carboplatin/Paclitaxel† (n = 402)
- Atezolizumab 1200 mg IV Q3W + Bevacizumab + Carboplatin/Paclitaxel† (n = 400)
- Bevacizumab + Carboplatin/Paclitaxel§ (n = 400)

- Maintenance†
  - Atezolizumab
  - Atezolizumab + Bevacizumab
  - Bevacizumab

- Atezolizumab until PD or loss of clinical benefit and/or bevacizumab until PD

- *If sensitizing EGFR mutation or ALK translocation present, must have PD on or intolerance to ≥ 1 approved targeted therapy. †Bevacizumab 15 mg/kg; carboplatin AUC 6; paclitaxel 200 mg/m²; all given IV Q3W for 4 or 6 cycles. ‡No crossover permitted. §Control arm.

- Coprimary endpoints: investigator-assessed PFS in ITT WT, Teff-high WT; OS in ITT WT
- Secondary endpoints: investigator-assessed PFS, OS in ITT; investigator-assessed PFS in PD-L1 subgroups; IRF-assessed PFS; ORR, DoR per RECIST v1.1; safety in ITT

Socinski MA, et al ASCO 2018
**IMpower150: Updated PFS in ITT WT Population**
*(Coprimary Endpoint)*

- **Atezolizumab + Bev + Carbo/Pac**
  - Median PFS, mos: 8.3 (7.7-9.8)
  - 6-mo PFS, %: 66
  - 12-mo PFS, %: 38
  - 18-mo PFS, %: 27

- **Bev + Carbo/Pac**
  - Median PFS, mos: 6.8 (6.0-7.1)
  - 6-mo PFS, %: 56
  - 12-mo PFS, %: 20
  - 18-mo PFS, %: 8

**HR: 0.59 (95% CI: 0.50-0.70; P < .0001)**

- Patients at Risk, n:
  - Atezolizumab + Bev + Carbo/Pac: 359
  - Bev + Carbo/Pac: 337

*ITT WT: patients without EGFR or ALK genetic alterations; 87% of randomized patients.*

**Median follow-up: ~ 20 mos.**

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**IMpower150: Interim OS in ITT WT Population**
*(Coprimary Endpoint)*

- **Atezolizumab + Bev + Carbo/Pac**
  - Patients, n: 359
  - Median OS, mos: 19.2 (17.0-23.8)
  - 12-mo OS, %: 67
  - 18-mo OS, %: 53
  - 24-mo OS, %: 43

- **Bev + Carbo/Pac**
  - Patients, n: 337
  - Median OS, mos: 14.7 (13.3-16.9)
  - 12-mo OS, %: 61
  - 18-mo OS, %: 41
  - 24-mo OS, %: 34

**HR: 0.78 (95% CI: 0.64-0.96; P = .0164)**

*ITT WT: patients without EGFR or ALK genetic alterations; 87% of randomized patients.*

- Median OS for atezolizumab + carbo/pac vs bev + carbo/pac: 19.4 vs 14.7 mos (HR: 0.88; P = .0241)
Second line immunotherapy

Approval of 3 PD-1/PD-L1 Inhibitors in Rapid Succession for Previously Treated Advanced NSCLC

Nivolumab FDA approved 2015

Atezolizumab FDA approved 2016


Slide credit: clinicaloptions.com
EGFR-positive NSCLC

Immunotherapy in *EGFR* Mutation–Positive Adv NSCLC

**CHECKMATE 057**
Nivolumab vs Docetaxel

**KEYNOTE-010**
Pembrolizumab vs Docetaxel

- Chemotherapy favored over IO for patients with *EGFR* mutations in second-line setting[1-4]
- In retrospective analysis, 3.6% response to PD-L1 pathway inhibitors (n = 28) compared with 23.3% (n = 30) in similar *EGFR* WT cohorts[5]
  - Few patients with both PD-L1 ≥ 5% and high CD8+ TILs (2%, n = 48)
- Retrospective analysis of PD-L1 expression in EGFR-mutant NSCLC found 49% of patients PD-L1 negative and only 8% with PD-L1 ≥ 50%, and TMB largely low[6]
  - Comparison for all NSCLC: PDL1 0% (34%), PDL1 1-49% (38%), PDL1≥50% (28%)

EGFR-positive NSCLC

CheckMate 012: Nivolumab + Ipilimumab in *EGFR* Mutation–Positive Advanced NSCLC

- Among *EGFR* mutation–positive patients receiving nivolumab + ipilimumab (n = 8): ORR 50%
  - PD-L1 ≥ 1%: 88%
  - PD-L1 ≥ 50%: 38%
- Tumor mutation burden unknown


Slide credit: clinicaloptions.com
Progression after Immunotherapy

Treatment Beyond Disease Progression: OAK

- 51\% of patients who progressed on atezolizumab continued beyond progression
  - 7\% (12/168) had subsequent PR;
  - 49\% (83/168) had stable disease

- Clinical characteristics similar at baseline and upon progression between those who continued atezolizumab or who switched to new treatments

- No increased safety risk in those treated beyond progression


Slide credit: clinicaloptions.com
Progression after Immunotherapy

Response to Subsequent Treatment After Immunotherapy in Advanced NSCLC: KEYNOTE-024

- KEYNOTE-024: patients with metastatic NSCLC PD-L1 ≥ 50% were randomized to received pembrolizumab or platinum-doublet chemotherapy
- After discontinuation, 45% of pembrolizumab patients (48/107) and 81% (97/120) of chemo patients went on to subsequent therapy; 66% (79/120) of patients who discontinued chemo crossed over to pembrolizumab
- Pembrolizumab showed continued OS benefit and improved PFS2 (time from randomization to progression on next-line treatment or death) with further follow-up

TMB in Lung Cancer

Schumacher and Schreiber, Science 2015
Is PDL > 1% a selection criterion in II line treatment?

CheckMate 227: Study Design

- Randomized, open-label, multipart phase III trial
  - Stratified by histology (squamous vs nonsquamous)
  - Up to 2 yrs

- Patients with stage IV or recurrent NSCLC, no previous systemic treatment, no known sensitizing EGFR/ALK alterations, ECOG PS 0/1 (N = 1739)
- ≥ 1% PD-L1 expression (n = 1189)
  - Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W (n = 396)
  - Histology-based CT* (n = 397)
  - Nivo 240 mg Q2W (n = 396)
- < 1% PD-L1 expression (n = 550)
  - Nivo 3 mg/kg Q2W + ipi 1 mg/kg Q6W (n = 187)
  - Histology-based CT* (n = 186)
  - Nivo 360 mg Q3W + histology-based CT* (n = 177)

- Co-primary endpoints: OS in PD-L1–selected populations, PFS in TMB-selected populations receiving nivolumab + ipilimumab vs CT
- Secondary endpoint (current analysis): PFS in patients with < 1% PD-L1 expression receiving nivolumab + CT vs CT

*Non-squamous: pem + cis or carbo Q3W for ≤ 4 cycles with optional maintenance (CT: nivolumab + CT; nivolumab + pem); squan gem + cis or carbo Q3W for ≤ 4 cycles.

1 patient randomized as < 1% PD-L1 and subsequently determined to have ≥ 1% PD-L1 expression.

CheckMate 227: Exploratory Analysis of PFS by TMB in Patients With < 1% PD-L1 Expression

**TMB ≥ 10 mut/Mb**

<table>
<thead>
<tr>
<th></th>
<th>Nivo + CT</th>
<th>Nivo + Ipi</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>43</td>
<td>38</td>
<td>48</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>6.2</td>
<td>7.7</td>
<td>5.3</td>
</tr>
<tr>
<td>HR vs CT (95% CI)</td>
<td>0.56 (0.35-0.91)</td>
<td>0.48 (0.27-0.85)</td>
<td>--</td>
</tr>
</tbody>
</table>

**TMB < 10 mut/Mb**

<table>
<thead>
<tr>
<th></th>
<th>Nivo + CT</th>
<th>Nivo + Ipi</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>54</td>
<td>52</td>
<td>59</td>
</tr>
<tr>
<td>Median PFS, mos</td>
<td>4.7</td>
<td>3.1</td>
<td>4.7</td>
</tr>
<tr>
<td>HR vs CT (95% CI)</td>
<td>0.87 (0.57-1.33)</td>
<td>1.17 (0.76-1.81)</td>
<td>--</td>
</tr>
</tbody>
</table>

**1-yr PFS: 45% (Nivo + CT)**

**1-yr PFS: 27% (Nivo + Ipi)**

**1-yr PFS: 8% (CT)**

**Patients at Risk, n**

<table>
<thead>
<tr>
<th></th>
<th>Nivo + CT</th>
<th>Nivo + Ipi</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo + CT</td>
<td>43</td>
<td>38</td>
<td>48</td>
</tr>
<tr>
<td>Nivo + Ipi</td>
<td>38</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>CT</td>
<td>48</td>
<td>30</td>
<td>16</td>
</tr>
</tbody>
</table>

**Patients at Risk, n**

<table>
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<td>52</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>CT</td>
<td>59</td>
<td>39</td>
<td>16</td>
</tr>
</tbody>
</table>

Borghaei H, et al. ASCO 2018
Not only CTLA-4 and PD-1/PD-L1

Pardoll et al., Nat Rev Cancer 2012
Need of patient selection

- Selection by PD-L1 expression
- Selection by Tumor Mutation Burden (TMB)
- Clinical Criteria
Unanswered Questions

➢ Are there some patients for whom immunotherapy with chemotherapy is superior to immunotherapy alone?

➢ Are combinations of immunotherapy going to be superior to a single agent?

➢ How do we integrate targeted agents?

➢ How do we deal with tumors once they've progressed after PD-1 monotherapy?
New Trials in NSCLC

<table>
<thead>
<tr>
<th>Sub group</th>
<th>ONCOGENE ADDICTED</th>
<th>OTHERS</th>
<th>HIGHLY SENSITIVE TO IMMUNO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR: gefitinib, erlotinib, afatinib, icotinib, dacotinib, osimertinib, pozoitinib (if EGFR exon 20 mut)</td>
<td><strong>NON SQUAMOUS</strong></td>
<td><strong>SQUAMOUS</strong></td>
<td>Pembrolizumab if PDL1 ≥ 50% tumor cells</td>
</tr>
<tr>
<td>ALK: crizotinib, ceritinib 750 mg, ceritinib 450 mg (low fat meal), alectinib, lorlatinib, ensartinib</td>
<td>Platinum-CT</td>
<td>Platinum-CT</td>
<td>Atezolizumab in TC 2/3 - IC 2/3 tumors</td>
</tr>
<tr>
<td>BRAF: dabrafenib + trametinib</td>
<td>Pemetrexed is an option</td>
<td>Necitumumab can be added</td>
<td>Avelumab in PD-L1 ≥ 1%</td>
</tr>
<tr>
<td>ROS1: crizotinib, ceritinib, entrectinib</td>
<td>Bevacizumab can be added</td>
<td>Nivolumab + ipilimumab</td>
<td>Durvalumab in PD-L1 ≥25%</td>
</tr>
<tr>
<td>MET: crizotinib</td>
<td>Pembrolizumab + platinum/pemetrexed (US)</td>
<td>Nivolumab + platinum CT</td>
<td>Nivolumab + Iplilimumab</td>
</tr>
<tr>
<td>NTRK: larotrectinib, entrectinib</td>
<td>Nivolumab + Iplilimumab</td>
<td>Nivolumab + platinum CT</td>
<td>Nivolumab + platinum CT</td>
</tr>
<tr>
<td><strong>Second And Further Line</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR: osimertinib if T790M+ EGFR+/MET+: savolitinib + osimertinib</td>
<td><strong>NON SQUAMOUS</strong></td>
<td></td>
<td>Pembrolizumab in PD-L1 ≥ 1% (if not administered in 1st line).</td>
</tr>
<tr>
<td>ALK: ceritinib 750 mg, ceritinib 450 mg (low fat meal), alectinib, brigatinib, lorlatinib, ensartinib</td>
<td>Docetaxel +/- nintedanib</td>
<td>Nivolumab</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>BRAF: dabrafenib + trametinib</td>
<td>Docetaxel +/- ramucirumab</td>
<td>Atezolizumab</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>RET: vandetanib, LOXO-292</td>
<td>Bevacizumab + Paclitaxel is an option in non-squamous (if Beva not administered in 1st line).</td>
<td>Avelumab</td>
<td>Durvalumab in PD-L1 ≥25%</td>
</tr>
<tr>
<td>HER2 : TDM-1</td>
<td>Nivolumab</td>
<td>Avelumab</td>
<td>Avelumab</td>
</tr>
<tr>
<td>ROS1: lorlatinib</td>
<td>Atezolizumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Phase I-II studies | Phase III studies

Roberto Ferrara et al. 2017 Scientific Advances in Thoracic Oncology
MMUNE-Mediated Adverse Events

**RESPIRATORY TRACT**
Signs and symptoms such as:
- Dyspnea
- Cough

**LIVER**
Signs such as:
- Increased hepatic values (e.g., AST, ALT or total bilirubin)

**GASTROINTESTINAL TRACT**
Signs and symptoms such as:
- Diarrhea
- Stomach pain
- Blood in stool

**ENDOCRINE SYSTEM**
Signs and symptoms such as:
- Fatigue
- Headache
- Psychological changes/mood swings
- Significant results for thyroid function tests and/or serum chemistry

Clinical manifestations – e.g. hypophysitis?
- Headache, visual symptoms
- Fatigue, weakness, nausea, anorexia, diarrhoea
- Loss of libido, polyuria, polydipsia
- Cold intolerance, dizziness, insomnia

Consider the potentially fatal nature of hypoadrenalism!
- Hypotension, hypoglycaemia or hyponatraemia
- The time to onset is usually about 9 weeks after initiation of therapy
Epilogue: How Immunotherapy has changed a patient’s life
Conclusions:

- Immunotherapy with immune checkpoints inhibitors has changed the way we treat and will treat many cancers, including NSCLC and (hopefully) SCLC.
- Response to ICI is related to the balance between innate (myeloid cells) and adaptive (T lymphocytes) immunity.
- More research is needed on predictive factors (PDL1, TMB) in order to extend the benefit of ICI.
- Combinations of ICIs, combinations of PD-1/PD-L1 inhibitors with chemo and radiotherapy, and dual blockade of IC and VEGF pathways are promising strategies.
- Beware of toxicities, mainly with combo regimens.
- Many trials ongoing and in preparation.
Acknowledgments