Immunotherapy in Non-Small Cell Lung Cancer (NSCLC)

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Disclosures (Updated April 2021)

- Research Funding: Astra-Zeneca
- Stocks
  - Fate Therapeutics, Merck, Exact Sciences, Blueprint Medicine, Gilead, Astra Zeneca, Novamax
Learning Objectives

- Introduction
- Describe the principles of cancer immunotherapy
- Discuss the role of immunotherapy for the treatment of NSCLC
- Identify which lung cancer patients would benefit from the initial use of immunotherapy versus chemo-immunotherapy
- Immune related adverse events
- Summary

Percent of Cases by Stage
- Localized: confined to primary site (57%)
- Regional: spread to regional lymph nodes (16%)
- Distant: cancer has metastasized (22%)
- Unknown: unstaged (5%)

5-Yr Relative Survival by Stage
- Localized: 56.3%
- Regional: 29.7%
- Distant: 4.7%
- Unstaged: 7.8%

Types of lung cancer and staging

Non-small cell lung cancer (NSCLC)

80% to 85% of lung cancers are NSCLC.

- Adenocarcinoma: Current or former smokers, or non-smokers, women > men, and younger people
- Squamous cell carcinoma: linked to a history of smoking
- Large cell (undifferentiated) carcinoma

Small cell lung cancer (SCLC)

~15% of lung cancer, strong smoking Hx and more aggressive
**Current Standard for NSCLC**

**NCCN Guidelines Version 4.2021**

**Non-Small Cell Lung Cancer**

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**CLINICAL PRESENTATION**

- Advanced or metastatic disease
  - Establish histologic subtype<sup>a</sup> with adequate tissue for molecular testing (consider rebiopsy<sup>kk</sup> if appropriate)
  - Smoking cessation counseling
  - Integrate palliative care<sup>c</sup> (See NCCN Guidelines for Palliative Care)

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**HISTOLOGIC SUBTYPE<sup>a</sup>**

- Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

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**BIOMARKER TESTING**

**Molecular testing, including:**
- EGFR mutation (category 1)
- ALK (category 1)
- ROS1, BRAF, NTRK1/2/3, METex14 skipping, RET

- Testing should be conducted as part of broad molecular profiling<sup>mm</sup>

- PD-L1 testing (category 1)

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**Squamous cell carcinoma**

**Consider molecular testing, including:**
- EGFR mutation
- ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping, RET

- Testing should be conducted as part of broad molecular profiling<sup>mm</sup>

- PD-L1 testing (category 1)

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**Key-**

- **PD-L1 testing** in all patients

- **Molecular testing** (look for oncogenic driver mutations) - all adenocarcinomas, select squamous cell
Non-Small-Cell Lung Cancer: Not One Disease, but Many!

Then Histology-Based Subtyping Now

- Adenocarcinoma
  - KRAS Sensitizing 17%
  - ALK 7%
  - EGFR Other 4%
  - MET 3%
  - > 1 Mutation 3%
  - HER2 2%
  - ROS1 2%
  - BRAF 2%
  - RET 2%
  - NTRK < 1%
  - PIK3CA 1%
  - MEK1 < 1%

- No Known Oncogenic Driver Detected 31%

- KRAS excluding G12C 12%

- Other 11%

- Squamous 34%

- Adenoca 55%

NSCLC as one disease

**Treatment Paradigm for Oncogenic mutation–Positive Advanced NSCLC**

- **Advanced NSCLC (molecular biomarker positive)**
  - **ALK** positive
    - Alectinib (preferred), brigatinib, ceritinib, or crizotinib
  - **ROS1** positive
    - Crizotinib or entrectinib
  - **BRAF V600E** positive
    - Dabrafenib/ trametinib
  - **NTRK** positive
    - Entrectinib or larotrectinib
  - **RET** positive
    - Selpercatinib or pralsetinib
  - **METex14** positive
    - Capmatinib

- **EGFR mutation positive**
  - Osimertinib (preferred), erlotinib, afatinib, gefitinib, or dacomitinib
  - Progression
    - **EGFR T790M** mutation positive
      - Osimertinib
    - **EGFR T790M** mutation negative or previous osimertinib
      - Alectinib, brigatinib, ceritinib, or lorlatinib dependent on previous therapy

Follow treatment options for adenocarcinoma or squamous cell carcinoma without actionable biomarker

*~ 35% of Patients With Advanced Nonsq NSCLC Have a Driver Mutation Targetable by an FDA-Approved Agent*
Treatment Paradigm for Advanced NSCLC with no oncogenic driver mutation

**Metastatic NSCLC**

- **Driver mutation**
- **PD-L1 testing**
  - **Molecular testing**
    - **PDL-1 negative**
      - Targeted therapy
      - Chemoimmunotherapy
    - **PDL-1 1-49%**
      - Chemoimmunotherapy (preferred)
      - Pembrolizumab alone
      - Nivolumab+Ipilimumab
    - **PDL-1 >50%**
      - Pembrolizumab or Atezolizumab or Cemiplimab alone (preferred)
      - Chemoimmunotherapy (select pts)

- **Wait for molecular testing results before initiating immunotherapy**
- **TAT-1 to 2 weeks**
- **Increase risk of pneumonitis with Immunotherapy->targeted therapy sequence**

**Immunotherapy is the backbone of treatment**

Chemoimmunotherapy= Pembrolizumab or atezolizumab or (Nivolumab+ipilimumab) with (carboplatin+paclitaxel or pemetrexed)
Cancer Immunotherapy

Cancer Immunotherapy is defined as the approach to treat the tumor by either inducing de novo or reactivating tumor specific immune responses.
Cancer Immunosurveillance

1. Release of cancer cell antigens
   - Immunogenic cell death
   - Tolerogenic cell death

2. Cancer antigen presentation
   - TNF-α
   - IL-1
   - IFN-α
   - CD40L/CD40
   - CDN
   - ATP
   - HMGB1
   - TLR
   - IL-10
   - IL-4
   - IL-13

3. Priming and activation
   - CD28/B7.1
   - CD137/CD137L
   - OX40/OX40L
   - CD27/CD70
   - HVEM
   - GITR
   - IL-2
   - IL-12
   - CTLA4/B7.1
   - PD-L1/PD-1
   - PD-L1/B7.1
   - Prostaglandins

4. Trafficking of T cells to tumors
   - CX3CL1
   - CXCL9
   - CXCL10
   - COL5

5. Infiltration of T cells into tumors
   - LFA1/ICAM1
   - Selectins
   - VEGF
   - Endothelin B receptor

6. Recognition of cancer cells by T cells
   - T cell receptor
   - Reduced pMHC on cancer cells

7. Killing of cancer cells
   - IFN-γ
   - T cell granule content
   - PD-L1/PD-1
   - LAG-3
   - Arginase
   - IDO
   - MICA/MICB
   - TGF-β1
   - B7-H4
   - BTLA
   - TIM-3/phospholipids
   - VISTA

Mellman et al Immunity 2013.
Immune checkpoints

- Ipilimumab, tremilimumab
- CTLA-4
- atezolizumab, durvalumab, avelumab
- PD-L1
- nivolumab, pembrolizumab, cemiplimab
- PD-1
Discovery of immune checkpoints

The Nobel Prize in Physiology or Medicine 2018

CTLA-4

James P. Allison
Prize share: 1/2

Tasuku Honjo
Prize share: 1/2

PD-L1

The Nobel Prize in Physiology or Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo "for their discovery of cancer therapy by inhibition of negative immune regulation."
Timeline of FDA approvals of immune checkpoint blockers
Current FDA Approvals of ICIs for Metastatic NSCLC

**Pembrolizumab**: PD during or following platinum-containing CT (and targeted therapy if EGFR or ALK positive) if PD-L1 TPS ≥ 1%

Pembrolizumab: 1L for metastatic NSCLC with tumor PD-L1 TPS ≥ 50%; no EGFR or ALK mut

Pembrolizumab in combination with platinum doublet CT as 1L for metastatic NSCLC; no EGFR or ALK mut

Nivolumab + ipilimumab: 1L for metastatic NSCLC with tumor PD-L1 expression ≥ 1%; no EGFR or ALK mut

Nivolumab + ipilimumab in combination with 2 cycles of platinum-doublet CT as 1L for metastatic NSCLC; no EGFR or ALK mut

Pembrolizumab: 1L for metastatic NSCLC with tumor PD-L1 TPS ≥ 1%; no EGFR or ALK mut

Pembrolizumab: 1L for metastatic NSCLC with tumor PD-L1 expression ≥ 1%; no EGFR or ALK mut

Pembrolizumab: 1L for metastatic NSCLC with tumor cell PD-L1 expression (TC) ≥ 50% or PD-L1 stained tumor-infiltrating immune cells (IC) ≥ 10% of the tumor area; no EGFR or ALK mut

Atezolizumab in combination with paclitaxel protein-bound/carboplatin as 1L for metastatic, non-squamous NSCLC; no EGFR or ALK mut

Atezolizumab in combination with bevacizumab/paclitaxel/carboplatin as 1L for metastatic, non-squamous NSCLC; no EGFR or ALK mut

Nivolumab: PD during or following platinum-containing CT (and targeted therapy if EGFR or ALK positive) if PD-L1 TPS ≥ 1%

Nivolumab: PD during or following platinum-containing CT (and targeted therapy if EGFR or ALK positive) if PD-L1 TPS ≥ 1%

Atezolizumab: PD during or following platinum-containing CT (and targeted therapy if EGFR or ALK mut)

Atezolizumab: PD during or following platinum-containing CT (and targeted therapy if EGFR or ALK mut)

Cemiplimab as 1L for metastatic NSCLC; PD-L1 >50%
Patient example

2/2015

- 58 yo father of 4 girls under 16
- Had 3 prior lung cancer surgeries
- Radiation therapy
- 2 lines of prior chemotherapy for metastatic disease

3/2015 - On trial with Atezolizumab

- Complete response
- After 3 years, stopped therapy
- As of today, has no evidence of disease
- He has outlived his wife and now is the primary caregiver for his 4 daughters
Treatment Paradigm for Advanced NSCLC with no driver mutation

**Metastatic NSCLC**

- **Driver mutation**
  - PDL-1 negative
    - Targeted therapy
      - Chemoimmunotherapy
  - PDL-1 1-49%
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**PD-L1 testing**

- Wait for molecular testing results before initiating immunotherapy
- TAT-1 to 2 weeks
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**Molecular testing**

- Wait for molecular testing results before initiating immunotherapy
- TAT-1 to 2 weeks
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**Chemoimmunotherapy**

Chemoimmunotherapy = Pembrolizumab or atezolizumab or (Nivolumab+ipilimumab) with (carboplatin+paclitaxel or pemetrexed)
Importance of level of PD-L1 expression

PDL-1 tumor proportion score (TPS)

Most robust biomarker
- By simple IHC
- PDL1 staining on tumor cells
- PD-L1 staining on immune cells used for atezolizumab

Topilan S, et al. NEJM 2012
# 4 drug approvals and 4 PD-L1 tests

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dako (22C3)</th>
<th>Dako (28-8)</th>
<th>Ventana SP263</th>
<th>Ventana SP 142</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>• Pembrolizumab</td>
<td>• Nivolumab</td>
<td>• Durvalumab</td>
<td>• Atezolizumab</td>
</tr>
<tr>
<td><strong>Staining pattern</strong></td>
<td>• Membranous (TC)</td>
<td>• Membranous (TC)</td>
<td>• Membranous (TC)</td>
<td>• Membranous (TC &amp; IC)</td>
</tr>
<tr>
<td><strong>IHC Staining</strong></td>
<td>• ≥50% (High)</td>
<td>• ≥1%</td>
<td>• ≥25% High - (Durvalumab)</td>
<td>• TC3/IC3 PD-L1 50% on TC or 10% IC (high)</td>
</tr>
<tr>
<td></td>
<td>• 1-49% (Low)</td>
<td>• ≥5%</td>
<td>• ≥10% (Nivolumab)</td>
<td>• TC 1/2 or IC 1/2 PD-L1 1-50% on TC and 1-10% on IC (low)</td>
</tr>
<tr>
<td></td>
<td>• &lt;1% (Neg)</td>
<td>• ≥10%</td>
<td></td>
<td>• TC 1/2/3 or IC 1/2/3 PD-L1 1-10% (Durvalumab)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• TC 0 or IC 0 PD-L1 &lt;1% on TC or IC (negative)</td>
</tr>
</tbody>
</table>

Pairwise comparison between assays for PD-L1 expression
demonstrated a high correlation.

22C3, 28-8, and SP263 assays demonstrated a high correlation.

All comparisons that include SP142 show lower correlation between assays.

Hirsch F et al. JTO 2016
4 drug approvals and 4 PD-L1 tests

Are there differences?
Pembrolizumab
KEYNOTE-024: First-line Pembrolizumab vs Platinum Doublet Chemotherapy for Advanced NSCLC PD-L1>50%

- Open-label, randomized phase III study

  Patients with untreated stage IV NSCLC; ECOG PS 0/1; no actionable EGFR/ALK aberrations; PD-L1 TPS ≥ 50%*; no untreated CNS mets or active autoimmune disease requiring tx (N = 305)

  Pembrolizumab 200 mg IV Q3W for up to 35 cycles (n = 154)

  Plt-doublet chemotherapy† (histology based) for 4-6 cycles (n = 151)

  Pembrolizumab 200 mg IV Q3W for up to 17 cycles

  PD (crossover allowed)

- Primary endpoint: PFS by BICR

- Secondary endpoints: ORR, OS, and safety

*≥ 50% tumor cell staining using 22C3 companion diagnostic IHC assay.
†Bevacizumab was not included, and maintenance was not required.

Stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and enrollment region

KEYNOTE-024: Survival With First-line Pembrolizumab vs Platinum Doublet Chemotherapy

PFS

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Median, Mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro (n = 154) 126 (81)</td>
<td>7.7 (6.1-10.2)</td>
</tr>
<tr>
<td>Chemo (n = 151) 141 (93)</td>
<td>5.5 (4.2-6.2)</td>
</tr>
</tbody>
</table>

HR: 0.50 (95% CI: 0.39-0.65)

OS

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Median, Mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro (n = 154) 103 (66.9)</td>
<td>26.3 (18.3-40.4)</td>
</tr>
<tr>
<td>Chemo (n = 151) 123 (81.5)</td>
<td>14.3 (9.4-18.3)</td>
</tr>
</tbody>
</table>

HR: 0.62 (95% CI: 0.48-0.81)

Patients at Risk, n

<table>
<thead>
<tr>
<th>Patients at Risk, n</th>
<th>Pembro</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>154</td>
<td>151</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
<td>73</td>
</tr>
<tr>
<td>12</td>
<td>62</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>24</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>36</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>42</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>48</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>54</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>66</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

FDA approval-2016

KEYNOTE-042: Study Design

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 (any histology); PD-L1 TPS ≥ 1%; EGFR/ALK neg; ECOG PS 0/1; no untreated/unstable CNS mets; no pneumonitis requiring steroids (N = 1274)

- Primary endpoint: OS in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%
- Secondary endpoints: PFS and ORR in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%; safety in ≥ 1%
- Current analysis planned for ~ 45 mos after study start

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

Carboplatin AUC 5 or 6 Q3W + Paclitaxel 200 mg/m² Q3W or Carboplatin AUC 5 or 6 Q3W + Pemetrexed 500 mg/m² Q3W up to 6 cycles (n = 637)
KEYNOTE-042: OS in TPS ≥ 50% and TPS ≥ 20% Patient Subgroups

**TPS ≥ 50%**

- **Pembrolizumab** 180 (60)
- **Chemo** 220 (73)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Pembrolizumab</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>300</td>
<td>231</td>
</tr>
<tr>
<td>Mos</td>
<td>190</td>
<td>151</td>
</tr>
<tr>
<td>PTs</td>
<td>157</td>
<td>113</td>
</tr>
<tr>
<td>Patients at Risk, n</td>
<td>Pembro</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>299</td>
<td>300</td>
</tr>
<tr>
<td></td>
<td>224</td>
<td>231</td>
</tr>
<tr>
<td></td>
<td>190</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td>157</td>
<td>113</td>
</tr>
<tr>
<td>Median OS, Mos (95% CI)</td>
<td>20.0 (15.9-24.2)</td>
<td>12.2 (10.4-14.6)</td>
</tr>
<tr>
<td>HR: 0.70 (95% CI: 0.58-0.86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TPS ≥ 20%**

- **Pembrolizumab** 261 (63)
- **Chemo** 296 (73)

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Pembrolizumab</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>206</td>
<td>113</td>
</tr>
<tr>
<td>Mos</td>
<td>155</td>
<td>80</td>
</tr>
<tr>
<td>PTs</td>
<td>121</td>
<td>40</td>
</tr>
<tr>
<td>Patients at Risk, n</td>
<td>Pembro</td>
<td>CT</td>
</tr>
<tr>
<td></td>
<td>413</td>
<td>405</td>
</tr>
<tr>
<td></td>
<td>305</td>
<td>313</td>
</tr>
<tr>
<td>Median OS, Mos (95% CI)</td>
<td>18.0 (15.4-21.9)</td>
<td>13.0 (11.6-15.3)</td>
</tr>
<tr>
<td>HR: 0.77 (95% CI: 0.65-0.91)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

KEYNOTE-042: OS in TPS ≥ 1% and TPS ≥1% to 49%

### Patient Subgroups

**TPS ≥ 1%**

<table>
<thead>
<tr>
<th>Events/Patients, n/(%)</th>
<th>Median OS, Mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>422 (66)</td>
</tr>
<tr>
<td>Chemo</td>
<td>481 (76)</td>
</tr>
</tbody>
</table>

**TPS ≥ 1% to 49%**

<table>
<thead>
<tr>
<th>Events/Patients, n/(%)</th>
<th>Median OS, Mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>242 (72)</td>
</tr>
<tr>
<td>Chemo</td>
<td>261 (77)</td>
</tr>
</tbody>
</table>

The benefit of pembrolizumab in the whole population was driven by patients with PD-L1 >50%

**FDA approval-2019**
KEYNOTE-189: First-line Carboplatin/Pemetrexed ± Pembrolizumab in Stage IV Nonsquamous NSCLC

- Randomized, double-blind, international phase III study

Stratified by PD-L1 TPS (≥ 1% vs < 1%), platinum agent (carboplatin vs cisplatin), smoking history (never vs former/current)

Patients with previously untreated, metastatic, nonsquamous NSCLC; ECOG PS 0/1; any PD-L1 status; no actionable EGFR/ALK mutations; no symptomatic CNS mets or pneumonitis requiring tx (N = 616)

- Primary endpoints: OS, PFS by BICR
- Secondary endpoints: ORR, DoR, safety

Gandhi. NEJM. 2018;378:2078.
KEYNOTE-189: OS

OS in ITT Population

HR for death: 0.49 (95% CI: 0.38-0.64; P < .001)

FDA approval-2018

Gandhi. NEJM. 2018;378:2078.
KEYNOTE-407: Carboplatin + Paclitaxel/nab-Paclitaxel ± Pembrolizumab in Advanced Squamous NSCLC

- Randomized, double-blind phase III trial
  - Stratified by PD-L1 TPS (< 1% vs ≥ 1%), taxane (paclitaxel vs nab-paclitaxel), region (east Asia vs other)

Patients with untreated stage IV squamous NSCLC; ECOG PS 0/1; available tumor biopsy for PD-L1 assessment; no symptomatic brain mets or pneumonitis requiring systemic steroids (N = 559)

- Pembrolizumab + Carboplatin + Paclitaxel or nab-Paclitaxel 3-wk cycles x 4 (n = 278)
- Pembrolizumab up to 31 cycles
- Placebo + Carboplatin + Paclitaxel or nab-Paclitaxel 3-wk cycles x 4 (n = 281)
- Placebo up to 31 cycles

Crossover allowed*

PD

- Pembrolizumab up to 35 cycles
- Placebo up to 31 cycles
- Pembrolizumab up to 35 cycles

Carboplatin AUC 6 Q3W; nab-paclitaxel 100 mg/m² QW or paclitaxel 200 mg/m² Q3W; pembrolizumab 200 mg Q3W.

*Upon confirmation of PD and safety criteria by BICR, optional crossover could occur during combination or monotherapy.

- Primary endpoint: PFS by RECIST v1.1 (BICR), OS
- Secondary endpoints: ORR and DoR by RECIST v1.1 (BICR), safety

Paz-Ares. NEJM. 2018;379:2040
KEYNOTE 407: OS

Paz Ares et al. ASCO 2018. 
Paz Ares. NEJM. 2018;379:2040. 

OS (ITT)

<table>
<thead>
<tr>
<th>Events, %</th>
<th>Median OS, Mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab + CT</td>
<td>30.6</td>
</tr>
<tr>
<td>Placebo + CT</td>
<td>42.7</td>
</tr>
</tbody>
</table>

HR: 0.64 (95% CI: 0.49-0.85; P = .0008)

FDA approval-2018
Nivolumab and ipilimumab
CheckMate 227: First-line Nivolumab + Low-Dose Ipilimumab for Advanced NSCLC

- Randomized, open-label, multipart phase III trial

- Stratified by histology (squamous vs nonsquamous)

- 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)
  - Platinum-doublet CT (n = 397)

- < 1% PD-L1 expression (n = 550)
  - Nivo 3 mg/kg Q2W + Ipi 1 mg/kg Q6W (n = 187)
  - Platinum-doublet CT (n = 186)

  - Nivo 360 mg Q3W + histology-based CT* (n = 177)

- Up to 2 yrs

- Coprimary endpoints for nivolumab + ipilimumab vs CT:
  - OS in patients with ≥ 1% PD-L1 expression
  - PFS in high TMB population

- Secondary endpoints: PFS and OS for nivolumab + CT vs CT in patients with PD-L1 < 1%; OS for nivolumab vs CT in patients with PD-L1 ≥ 50%
CheckMate 227: OS by Biomarker Status

OS in Patients With ≥ 1% PD-L1 Expression

Patients, n  Median OS, Mos
Nivo + ipi  396  17.1
CT  397  14.9

HR: 0.79
(97.72% CI: 0.65-0.96; P = .007)
Median f/u: 29.3 mos

1-yr OS
63% vs 56%

2-yr OS
40% vs 33%

Patients at Risk, n
Nivo + ipi  CT
396  397
341  358
295  306
264  250
244  218
212  190
190  166
165  141
153  126
145  93
129  57
91  22
41  6
9  1
1  0

FDA approval-2020; only PD-L1 positive patients

<table>
<thead>
<tr>
<th>Median OS, Mos</th>
<th>Nivo + Ipi</th>
<th>CT</th>
<th>HR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1% (n = 373)</td>
<td>17.2</td>
<td>12.2</td>
<td>0.62</td>
</tr>
<tr>
<td>1% to 49% (n = 396)\†</td>
<td>15.1</td>
<td>15.1</td>
<td>0.94</td>
</tr>
<tr>
<td>≥ 50% (n = 397)\‡</td>
<td>21.2</td>
<td>14.0</td>
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<tr>
<td>TMB</td>
<td></td>
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</tr>
<tr>
<td>&lt; 10 Mut/Mb (n = 380)\†</td>
<td>16.2</td>
<td>12.6</td>
<td>0.75</td>
</tr>
<tr>
<td>≥ 10 Mut/Mb (n = 299)\‡</td>
<td>23.0</td>
<td>16.4</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*Unstratified. †Exploratory subgroup analyses.
CheckMate 9LA: Study Design

- Randomized, open-label, phase III study

- Primary endpoint: OS

- Secondary endpoints: PFS, ORR, efficacy by tumor PD-L1 expression

Patients with stage IV or recurrent NSCLC, no previous systemic Tx, no sensitizing EGFR/ALK alterations, ECOG PS 0/1 (N = 719)

Nivo 360 mg Q3W + Ipi 1 mg/kg Q6W + CT* Q3W (2 cycles) (n = 361)

CT* Q3W (4 cycles)
Optional pemetrexed maintenance (NSQ) (n = 358)

*Pts with NSQ: pemetrexed + cisplatin or carboplatin; pts with SQ: paclitaxel + carboplatin.

Until PD, unacceptable toxicity, or for 2 yrs for immunotherapy

Stratified by PD-L1 expression (≥ 1% vs < 1%), sex, and histology (squamous vs nonsquamous)

CheckMate 9LA: Interim and Updated OS Results

- Interim analysis (minimum FU 8.1 mos) median OS, Nivo + Ipi + CT vs CT: 14.1 vs 10.7 mos; HR: 0.69 (95% CI: 0.55-0.87); $P = .0006$; met primary endpoint

- Updated results (minimum FU 12.7 mos)

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Median OS, mos (95% CI)</th>
<th>HR: 0.66 (95% CI: 0.55-0.80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo + Ipi + CT</td>
<td>361</td>
<td>15.6 (13.9-20.0)</td>
</tr>
<tr>
<td>Chemo</td>
<td>358</td>
<td>10.9 (9.5-12.6)</td>
</tr>
</tbody>
</table>

No. at risk

- Nivo + Ipi + CT: 361, 326, 292, 250, 227, 153, 86, 33, 10, 1, 0
- Chemo: 358, 319, 260, 208, 166, 116, 67, 26, 11, 0, 0

FDA approval-2020-(irrespective of PD-L1 status)
CheckMate 9LA: OS By PD-L1 Expression

For PD-L1 < 1%:
- HR 0.62 (0.45-0.85)
- Nivo + Ipi + CT
- CT

For PD-L1 ≥ 1%:
- HR 0.64 (0.50-0.82)
- Nivo + Ipi + CT
- CT

For PD-L1 1-49%:
- HR 0.61 (0.44-0.84)
- Nivo + Ipi + CT
- CT

For PD-L1 ≥ 50%:
- HR 0.66 (0.44-0.99)
- Nivo + Ipi + CT
- CT

Atezolizumab
**IMpower150**

- **IMpower150**: Multicenter, open-label, randomized phase III trial
  
  *Stratified by sex, PD-L1 expression, liver metastases*

- 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

---

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**

*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.

---

IMpower150

Rate of Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>At 12 mo</th>
<th>At 24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCP</td>
<td>67.3% (95% CI, 62.4–72.2)</td>
<td>43.4% (95% CI, 36.9–49.9)</td>
</tr>
<tr>
<td>BCP</td>
<td>60.6% (95% CI, 55.3–65.9)</td>
<td>33.7% (95% CI, 27.4–40.0)</td>
</tr>
</tbody>
</table>

Stratified hazard ratio: 0.78 (95% CI, 0.64–0.96)  
P = 0.02

No. at Risk

<table>
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<tr>
<th></th>
<th>ABCP</th>
<th>BCP</th>
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FDA approval-2019
Atezolizumab in Chemotherapy-Naive Metastatic NSCLC (IMpower110): Phase III Study Design

- **Primary endpoint:** OS in WT population (excluding patients with EGFR+ and/or ALK+ NSCLC)
- **Secondary endpoints:** investigator-assessed PFS, ORR and DoR (per RECIST v1.1)

**Stratified by sex, PS, PD-L1 expression, histology**

- Chemotherapy-naive patients with stage IV NSCLC with PD-L1 ≥ 1% on TC/IC (SP142 assay) (N = 572)

  - **Nonsquamous histology**: Cisplatin or Carboplatin + Pemetrexed
  - **Squamous histology**: Cisplatin or Carboplatin + Gemcitabine

**Maintenance therapy (no crossover)**

- Atezolizumab 1200 mg Q3W
  - PD or loss of clinical benefit

- Pemetrexed
  - PD

- Best supportive care
  - PD

*Cisplatin 75 mg/m² or carboplatin AUC 6 + pemetrexed 500 mg/m² IV Q3W for 4 or 6 cycles.
†Cisplatin 75mg/m² + gemcitabine 1250 mg/m² IV Q3W or carboplatin AUC5 + gemcitabine 1000 mg/m² IV Q3W for 4 or 6 cycles.

**IMpower110: OS for TC3 or IC3 WT Patients**

- **Atezolizumab (n = 107)**
  - 6-Mo OS: 76.3% (95% CI: 68.2-84.4)
  - 12-Mo OS: 64.9% (95% CI: 55.4-74.4)
  - HR: 0.59 (95% CI: 0.40-0.89; P = .0106)
  - Median follow-up: 15.7 mos (range: 0-35)

- **Chemotherapy (n = 98)**
  - 6-Mo OS: 70.1% (95% CI: 60.8-79.4)
  - 12-Mo OS: 50.6% (95% CI: 40.0-61.3)
  - Median OS: 13.1 mos (95% CI: 7.4-16.5)
  - Median OS: 20.2 mos (95% CI: 16.5-NE)

**Patients at Risk, n**

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<tr>
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</table>

IMpower110: OS for TC2/3 or IC2/3 WT Patients

6-Mo OS (95% CI) | 12-Mo OS (95% CI)
---|---
Atezolizumab (n = 166) | 79.3 (73.1-85.5) | 60.7 (52.6-68.7)
Chemotherapy (n = 162) | 76.1 (69.3-82.8) | 56.0 (47.7-64.3)

HR: 0.72 (95% CI: 0.52-0.99; P = .0416)

Median follow-up: 15.2 mos (range: 0-35)


FDA approval-2020-(only in high-PD-L1)
Cemiplimab
EMPOWER-Lung 1: Exploratory Analysis of Outcomes by PD-L1 Expression

- In phase III EMPOWER-Lung 1 trial, first-line cemiplimab monotherapy showed superior median OS and PFS, higher ORR and longer DoR vs standard chemotherapy in advanced NSCLC patients with PD-L1 ≥ 50%[1]
  
  - Exploratory analysis examined clinical outcomes by PD-L1 expression level in prespecified PD-L1 ≥ 50% cohort[2,3]

**Cemiplimab 350 mg Q3W Until PD or 108 wks**

- Until PD or 108 wks
- PD: May continue cemiplimab + 4 cycles chemotherapy
- PD: Crossover allowed to cemiplimab monotherapy

**Chemotherapy 4-6 cycles investigator’s choice**

- Patients with treatment naive advanced NSCLC, PD-L1 ≥ 50%, no EGFR/ALK/ROS1 mutations, ECOG PS 0/1 (N = 710)[1-3]
- Stratified by histology and geographical region (Europe, Asia, ROW)

**Exploratory Analysis Cohort[2,3]**

- Testing according to instructions for use at entry (n = 475)*
- Testing not according to instructions; PD-L1 ≥ 50% on retest (n = 88)

**Total PD-L1 ≥ 50% cohort n = 563†**

- Primary endpoints: OS and PFS[1-3]

- Secondary endpoints: ORR, DoR, HRQoL, and safety[1-3]

---

*Enrolled after August 2018 and not subject to PD-L1 retesting because initial test performed according to the assay's instructions for use.

†Prespecified cohort consisting of patients with testing according to instructions and patients with PD-L1 ≥ 50% on retest.

EMPOWER-Lung 1 in PD-L1 ≥ 50% NSCLC: Efficacy

- Cemiplimab monotherapy: superior median OS/PFS vs chemotherapy in PD-L1 ≥ 50% subpopulation

### OS

- Median, Mos (95% CI): Cemiplimab (N=475) vs Chemotherapy (N=475)
  - NR (NE-NE) vs 12.1 (10.2-17.5) HR (95% CI): 0.57 (0.40-0.80)

- Median, Mos (95% CI): Cemiplimab (N=563) vs Chemotherapy (N=563)
  - NR (17.9-NE) vs 14.2 (11.2-17.5) HR (95% CI): 0.57 (0.42-0.77)

- 12-Mo OS, % (95% CI): 71.5 (63.7-77.9) vs 50.8 (41.8-59.1)
  - 72.4 (65.6-78.1) vs 53.9 (46.2-61.1)

### PFS

- Median, Mos (95% CI): Cemiplimab (N=475) vs Chemotherapy (N=475)
  - 6.3 (4.5-8.5) vs 5.6 (4.3-6.2) HR (95% CI): 0.60 (0.47-0.77)

- Median, Mos (95% CI): Cemiplimab (N=563) vs Chemotherapy (N=563)
  - 8.2 (6.1-8.8) vs 5.7 (4.5-6.2) HR (95% CI): 0.54 (0.43-0.68)

### FDA approval-2021-(PD-L1 > 50%)

Kilickap. WCLC 2020. Abstr OA01.03. Reproduced with permission.
KEYNOTE-598: First-line Pembrolizumab ± Ipilimumab for Metastatic NSCLC With PD-L1 TPS ≥ 50%

- Double-blind, randomized phase III study

Patients with untreated stage IV NSCLC; ECOG PS 0/1; no actionable EGFR/ALK aberrations; PD-L1 TPS ≥ 50%;* no untreated CNS mets; ≥ 1 lesion measurable per RECIST v1.1 (N = 568)

Stratified by ECOG PS (0 vs 1), histology (squamous vs nonsquamous), and region (East Asia vs others)

Pembrolizumab 200 mg Q3W for ≤ 35 doses + Ipilimumab 1 mg/kg Q6W for ≤ 18 doses (n = 284)

Pembrolizumab 200 mg Q3W for ≤ 35 doses + Placebo Q6W for up to 18 doses (n = 284)

*Assessed centrally using the PD-L1 IHC 22C3 pharmDx assay.

- Primary endpoints: OS and PFS per RECIST v1.1 by BICR
- Key secondary endpoints: ORR and DoR per RECIST v1.1 by BICR, safety
## KEYNOTE-598: OS and PFS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pembrolizumab + Ipilimumab (n = 284)</th>
<th>Pembrolizumab + Placebo (n = 284)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, mos</td>
<td>21.4</td>
<td>21.9</td>
<td></td>
</tr>
<tr>
<td>12-mo rate, %</td>
<td>63.6</td>
<td>67.9</td>
<td>1.08 (0.85-1.37; P = .74)</td>
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<tr>
<td>Patients with event, %</td>
<td>48.2</td>
<td>47.5</td>
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</tr>
<tr>
<td>RMST at 24 mos, mos</td>
<td>16.09</td>
<td>16.61</td>
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<tr>
<td>RMST at maximum time, mos</td>
<td>18.76</td>
<td>19.32</td>
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<tr>
<td>Median PFS, mos</td>
<td>8.2</td>
<td>8.4</td>
<td>1.06 (0.86-1.30; P = .72)</td>
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<tr>
<td>12-mo rate, %</td>
<td>41.3</td>
<td>42.1</td>
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<tr>
<td>Patients with event, %</td>
<td>66.2</td>
<td>64.8</td>
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</tbody>
</table>

No benefit of adding ipilimumab to pembrolizumab in PD-L1 >50%
Immune Checkpoint Inhibitors in Stage III NSCLC
PACIFIC: Consolidation Durvalumab After Concurrent CRT for Locally Advanced, Unresectable, Stage III NSCLC

- Randomized, double-blind, placebo-controlled phase III trial

*Patients with locally advanced, unresectable, stage III NSCLC without PD after definitive platinum-based concurrent CRT* (≥ 2 cycles); WHO PS 0/1; life expectancy ≥ 12 wks (N = 713)

- Durvalumab 10 mg/kg IV Q2W for up to 12 mos (n = 476)
- Placebo IV Q2W for up to 12 mos (n = 237)

Stratified by age (< 65 vs ≥ 65 yrs), sex (male vs female), and smoking history (current/former vs never)

- Primary endpoints: PFS by BICR per RECIST v1.1, OS
- Secondary endpoints including ORR, DoR, TTDM, PFS2, safety/tolerability, PROs

*Any platinum-based chemotherapy regimen; 54-66 Gy RT.
PACIFIC: PFS and OS with Durvalumab at 4 Yrs

**Updated PFS (BICR; ITT)**

<table>
<thead>
<tr>
<th></th>
<th>No. of Events/Total No. of Patients (%)</th>
<th>Median PFS, Mos (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Durvalumab</td>
<td>266/476 (55.9)</td>
<td>17.2 (12.3-23.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>174/237 (73.4)</td>
<td>5.6 (4.6-7.7)</td>
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</tbody>
</table>

Stratified HR: 0.55 (95% CI: 0.44-0.67)
Stratified HR from primary analysis: 0.52 (95% CI: 0.42-0.65)

**Updated OS (ITT)**

<table>
<thead>
<tr>
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<th>No. of Events/Total No. of Patients (%)</th>
<th>Median OS,Mos (95% CI)</th>
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<tr>
<td>Durvalumab</td>
<td>247/476 (51.9)</td>
<td>47.5 (38.4-52.6)</td>
</tr>
<tr>
<td>Placebo</td>
<td>149/237 (62.9)</td>
<td>29.1 (22.1-35.1)</td>
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Stratified HR: 0.71 (95% CI: 0.57-0.88)
Stratified HR from primary analysis: 0.68 (95% CI: 0.53-0.87)

FDA approval-2018
Immune related adverse events (irAE)
Immune-Related AEs Throughout the Body

- There are unique AEs associated with immune checkpoint inhibitor therapy.
- These represent a new spectrum of AEs that differ in important ways from those associated with chemotherapy and targeted agents.
  - Immune-related AEs occur through an imbalance of tolerance and drug-induced immunity (auto-immunity).
ICI Treatment and irAEs: Basic Issues

- Most but not all irAEs occur during the first 12 wks of therapy (ie, during induction therapy)
- Early recognition and treatment is the key
- Steroids can be used to manage almost all irAEs
- Prolonged steroid tapers are usually required
- irAEs can wax and wane, particularly colitis or hepatitis
- Late irAEs can occur: even months after drug is stopped

Onset of Grade 3/4 Immune-Related AEs With Nivolumab + Ipilimumab vs Nivolumab

<table>
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<th>Nivolumab</th>
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<td>Skin (n = 18)</td>
<td>5.6 (0.1-55.0)</td>
<td>19.4 (1.3-50.9)</td>
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<td>19.4 (1.3-50.9)</td>
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<td>Gastrointestinal (n = 46)</td>
<td>7.4 (1.0-48.9)</td>
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<td>26.3 (13.1-57.0)</td>
<td>7.4 (1.0-48.9)</td>
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<td>Endocrine (n = 15)</td>
<td>12.1 (2.9-17.0)</td>
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<td>12.1 (2.9-17.0)</td>
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<td>14.1 (1.9-25.1)</td>
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<td>Pulmonary (n = 3)</td>
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<td>Renal (n = 6)</td>
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<td>50.9 (50.9-50.9)</td>
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<td>50.9 (50.9-50.9)</td>
<td>11.3 (3.3-23.7)</td>
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# General Management of irAEs Associated With Immune Checkpoint Inhibitors

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<thead>
<tr>
<th>Grade</th>
<th>Steroids</th>
<th>Treatment</th>
<th>Persistent/Recurring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Treat symptomatically; no systemic steroids</td>
<td>Can continue</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Steroids for selected irAEs and for recurrent irAEs</td>
<td>Continue, Hold for selected irAEs</td>
<td>Systemic steroids, Consider withholding; discontinue if ≥ 12 wks</td>
</tr>
<tr>
<td>3</td>
<td>Systemic steroids, prolonged tapers</td>
<td>Withhold or discontinue*</td>
<td>Systemic steroids and discontinue</td>
</tr>
<tr>
<td>4</td>
<td>High-grade systemic steroids, prolonged tapers</td>
<td>Discontinue (unless endocrine irAE)</td>
<td>Add other immune suppressants</td>
</tr>
</tbody>
</table>

*Discontinue for grade 3 irAEs renal toxicity, pneumonitis, and infusion reactions; question for grade 3 hepatotoxicity.

Selected AEs: colitis, pneumonitis, liver/renal toxicity, hypophysitis, neurologic

Systemic steroids (PO or IV): 1-2 mg/kg/day prednisone or equivalent
- Slow taper over ≥ 4 wks recommended
- Several courses may be necessary if symptoms worsen when dose decreased

Immunotherapy in challenging populations

These patients are usually excluded from clinical trials

- Patients with oncogenic driver mutations (some date in EGFR/ALK+, IMPOWER 150)
- Patients with active auto-immune disorders
- Patients on chronic immunosuppressives (organ transplant patients)
- Poor performance status (ECOG PS 3, 4)
- Pregnancy (Category D)
What if immunotherapy does not work?

- Response rates can vary from 30% to 60%
- 75-80% of patients will ultimately progress
- How to stimulate/reinvigorate immune response?
Summary

- Immunotherapy is the backbone of treatment in patients with advanced NSCLC with no oncogenic driver mutations.
- PD-L1 >50% - Single agent immunotherapy is appropriate.
- PD-L1 1-49% or <1% - Addition of chemotherapy has best outcomes.
- Immune related side-effects are common, early recognition is the key.
- Ongoing studies to integrate immunotherapy in localized NSCLC.
- Resistance mechanisms to immunotherapy is an active area of research.
The real reason dinosaurs became extinct