Learning Objectives

Upon completion, participants should be able to:

• Interpret new developments in the use of radiation therapy in non–small cell lung cancer

• Integrate current clinical evidence on the role of surgery in treating early and locally advanced non–small cell lung cancer into treatment decisions for appropriate patients

• Outline key current evidence that affects clinical practice and the care of patients with advanced non–small cell lung cancer
Advances in RT for Thoracic Malignancies

Christopher Kelsey, MD

Brain Metastases, RT, and Immune CPIs

SRS: 20 Gy X 1

2 months

Photos courtesy of Christopher Kelsey, MD.
Higher Risk of CNS-AEs After Treatment With CNS-RT Plus CPIs

- Patients with melanoma or NSCLC with brain metastases (N = 213) treated with CNS-RT (SRS or WBRT) +/- immune CPIs
  - 28 with CPIs
  - 184 without CPIs
- CNS-AEs: new or increasing edema (without disease progression), new or worsening neurologic deficits
  - Need to start or increase corticosteroids


Higher Risk of CNS-AEs After Treatment With CNS-RT Plus CPIs

- NSCLC (78%), SRS (69%), median size 1.7 cm
- CNS-AEs, n = 40 (19%)
  - Neurologic deficit in 22 (55%)
- CPIs within 3 months of brain RT only factor associated with increased risk of CNS-AEs (OR, 3.9; 95% CI, 1.6-9.2; \( P = .002 \))
- 11/28 (39%) with CPIs vs 29/184 (16%) without CPIs

ETOP NICOLAS Phase 2 Trial

- Patients (N = 62) with stage III NSCLC
- 3 cycles of platinum-based chemotherapy and definitive RT (66 Gy) with concurrent nivolumab
- Primary endpoint: grade ≥ 3 pneumonitis at 6 months post-RT with interim analysis after 21 patients
- No grade ≥ 3 pneumonitis in first 21 patients (3-month follow-up)
  - 6 (10%) grade 3 pneumonitis (2 > 6 months after RT)
- Study ongoing (1-year PFS secondary endpoint)
PEMBRO-RT Study (Netherlands)

- Hypothesis:
  - High-dose RT can lead to increased tumor antigen release, improved antigen presentation, and T-cell infiltration
  - SBRT to a single metastatic site preceding pembrolizumab would lead to increased tumor response in stage IV NSCLC

- Patients (n = 64) with stage IV NSCLC (≥ 2nd line) regardless of PD-L1 status randomized to:
  - Pembrolizumab (200 mg Q3W)
  - SBRT (8 Gy X 3) to a single metastasis →pembrolizumab

- ORR (12 weeks): 21% vs 39% (P = .28)
- Median PFS: 2.8 months vs 7.1 months
  - Most significant improvement in PD-L1: 0%
- No increased toxicity
SBRT for Operable Stage I NSCLC (Japan)

- Patients (n = 64) with operable, cT1N0 NSCLC received SBRT (12 Gy X 4 at isocenter); primary endpoint: 3-year OS (80%)
- Median age: 79 years
- OS was 77% (3 years), 54% (5 years), and 24% (10 years)
- 27 failures (9 local failures, 11 regional nodal failures, 11 distant metastases)
- Grade 3 toxicity in 6 patients (9%); chest pain (n = 1), dyspnea (n = 4), hypoxia (n = 1), pneumonitis (n = 2)

SBRT vs Surgery Trials

- Veterans Affairs: VALOR
  - SBRT vs lobectomy/segmentectomy
  - Watch videos followed by TSU and rad onc consults
- United Kingdom: SABRTooth
  - Initial meeting with pulmonologist
- UT Southwestern: STABLE-MATES
  - SBRT vs sublobar resection (high-risk surgical population)
  - Pre-randomization before protocol discussion


Overview

• Revisiting the role of surgery in the management of SCLC
• The debate: surgery vs radiation for stage I lung cancer
• Open surgery vs VATS and long-term OS
• Surgery in the new era of immunotherapy
Surgery Should Be Considered in Early Stage SCLC


Surgery vs Concurrent ChemoRT

- 54 (46.1 to 64.1) months
- 48.1% (43.5% to 52.3%)

Concurrent chemoRT

- 25.8 (24.0 to 28.2) months
- 28.3% (25.0% to 30.8%)

OS, probability

<table>
<thead>
<tr>
<th></th>
<th>Median survival (95% CI)</th>
<th>5-year survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>54.9 (46.1 to 64.1) months</td>
<td>48.1% (43.5% to 52.3%)</td>
</tr>
<tr>
<td>Concurrent chemoRT</td>
<td>25.8 (24.0 to 28.2) months</td>
<td>28.3% (25.0% to 30.8%)</td>
</tr>
</tbody>
</table>

Log-rank P < .01

Surgical Resection:
Safe After Induction Immunotherapy

- Neoadjuvant chemotherapy and ipilimumab followed by surgery
  - 13 patients with stage II-IIIA NSCLC
  - Zero 30-day mortalities
  - No increase in perioperative complications
    - Compared with historical cohort of patients (n = 42) who received preoperative therapy with platinum doublet

- Neoadjuvant nivolumab followed by surgery
  - 21 patients with resectable early NSCLC
  - Zero delays in surgery
  - Major pathologic response in 45% of tumors

Wedge Resection vs Radiation: Better Survival With Surgery


OS: VATS Is Noninferior to Open Surgery

Phase 3 Trials of Immunotherapy for Advanced NSCLC

Thomas Eldridge Stinchcombe, MD

KEYNOTE-407 Study Design

Key Eligibility Criteria
- Untreated stage IV NSCLC with squamous histology
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Pembrolizumab 200 mg Q3W + carboplatin AUC 6 Q3W + paclitaxel 200 mg/m² Q3W OR nab-paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 weeks)
Placebo (normal saline) Q3W + carboplatin AUC 6 Q3W + paclitaxel 200 mg/m² Q3W OR nab-paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wks)

R (1:1)

Pembrolizumab 200 mg Q3W for up to 31 cycles
Placebo (normal saline) Q3W for up to 31 cycles

Optional Crossover
Pembrolizumab 200 mg Q3W for up to 35 cycles

Endpoints
- Primary: PFS (RECIST v1.1, BICR) and OS
- Secondary: ORR and DOR (RECIST v1.1, BICR), safety

Stratification Factors
- PD-L1 expression (TPS < 1% vs ≥ 1%)
- Choice of taxane (paclitaxel vs nab-paclitaxel)
- Geographic region (east Asia vs rest of world)

aPercentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
bPatients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR, and all safety criteria had to be met.
### OS at IA2, ITT

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>30.6%</td>
<td>0.64</td>
<td>.0008</td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>42.7%</td>
<td>(0.49-0.85)</td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff date: April 3, 2018.
Please see full prescribing information for warnings, efficacy, risk, and safety.

### OS at IA2 by PD-L1 TPS

#### TPS < 1%

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>30.5%</td>
<td>0.61 (0.38-0.96)</td>
<td></td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>44.4%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)

- Pembro + chemo: 15.9 mo (13.1-NE)
- Placebo + chemo: 10.2 mo (8.6-12.8)

#### TPS 1%-49%

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>30.1%</td>
<td>0.57 (0.36-0.90)</td>
<td></td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>43.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)

- Pembro + chemo: 14.0 mo (12.8-NE)
- Placebo + chemo: 11.6 mo (8.9-17.2)

#### TPS ≥ 50%

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + chemo</td>
<td>31.5%</td>
<td>0.64 (0.37-1.10)</td>
<td></td>
</tr>
<tr>
<td>Placebo + chemo</td>
<td>41.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)

- Pembro + chemo: 15.9 mo (11.3 mo-NE)
- Placebo + chemo: 11.6 mo (7.4 mo-NE)

Please see full prescribing information for warnings, efficacy, risk, and safety.
**IMpower150 Study Design**

### Key Eligibility Criteria
- Stage IV or recurrent metastatic non-squamous NSCLC
- Chemotherapy-naive
- Tumor tissue available for biomarker testing
- Any PD-L1 IHC status

### Stratification Factors
- Sex
- PD-L1 IHC expression
- Liver metastases

#### Maintenance therapy (no crossover permitted)

- **Arm A**: Atezolizumab\(^a\) + carboplatin\(^2\) + paclitaxel\(^3\) for 4 or 6 cycles
- **Arm B**: Atezolizumab\(^4\) + carboplatin\(^2\) + paclitaxel\(^3\) + bevacizumab\(^4\) for 4 or 6 cycles
- **Arm C (control)**: Carboplatin\(^2\) + paclitaxel\(^3\) + bevacizumab\(^4\) for 4 or 6 cycles

#### Treatment Protocols

- **Arm A**: Atezolizumab + carboplatin + paclitaxel for 4 or 6 cycles
- **Arm B**: Atezolizumab + carboplatin + paclitaxel + bevacizumab for 4 or 6 cycles
- **Arm C (control)**: Carboplatin + paclitaxel + bevacizumab for 4 or 6 cycles

### Enrollment

N = 1,202

---

**OS in the ITT-WT**

<table>
<thead>
<tr>
<th>Landmark OS, %</th>
<th>Arm B: Atezo + bev + CP</th>
<th>Arm C: Bev + CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-month</td>
<td>67%</td>
<td>61%</td>
</tr>
<tr>
<td>18-month</td>
<td>53%</td>
<td>41%</td>
</tr>
<tr>
<td>24-month</td>
<td>43%</td>
<td>34%</td>
</tr>
</tbody>
</table>

HR\(^a\), 0.78  
(95% CI: 0.64, 0.96)  
\(P = .0164\)  
Median follow-up: ~20 mo

---

\(\text{HR}^a\), 0.78  
(95% CI: 0.64, 0.96)  
\(P = .0164\)  
Median follow-up: ~20 mo

---

\(^a\)Patients with a sensitizing EGFR mutation or ALK translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies.

\(\text{Atezolizumab: 1200 mg IV Q3W. Carboplatin: AUC 6 IV Q3W. Paclitaxel: 200 mg/m}^2 \text{ IV Q3W. Bevacizumab: 15 mg/kg IV Q3W.} \)


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Please see full prescribing information for warnings, efficacy, risk, and safety.
OS in Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>Median OS, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1–high (TC3 or IC3) WT</td>
<td>136 (20%)</td>
<td>25.2</td>
</tr>
<tr>
<td>PD-L1–low (TC1/2 or IC1/2) WT</td>
<td>226 (32%)</td>
<td>20.3</td>
</tr>
<tr>
<td>PD-L1–negative (TC0 and IC0) WT</td>
<td>339 (49%)</td>
<td>17.1</td>
</tr>
<tr>
<td>Liver metastases WT</td>
<td>94 (14%)</td>
<td>13.2</td>
</tr>
<tr>
<td>No liver metastases WT</td>
<td>602 (86%)</td>
<td>19.8</td>
</tr>
<tr>
<td>ITT (including EGFR/ALK+)</td>
<td>800 (100%)</td>
<td>19.8</td>
</tr>
<tr>
<td>EGFR/ALK+ only</td>
<td>104 (13%)</td>
<td>NE</td>
</tr>
<tr>
<td>ITT-WT</td>
<td>696 (87%)</td>
<td>19.2</td>
</tr>
</tbody>
</table>

*Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n = 696); prevalence of ITT, EGFR/ALK+, and ITT-WT out of ITT (n = 800). *One patient had EGFR exon 19 deletion and also tested ALK positive per central lab. *Stratified HR for ITT and ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018.

KEYNOTE-042 Study Design

Key Eligibility Criteria
- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS ≥ 1%
- No sensitizing EGFR or ALK alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification Factors
- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS (≥ 50% vs 1%-49%)

Endpoints
- Primary: OS in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%
- Secondary: PFS and ORR in TPS ≥ 50%, ≥ 20%, and ≥ 1%; safety in TPS ≥ 1%

*Pemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

OS: TPS ≥ 1%

**Events** | **HR (95% CI)** | **P**
--- | --- | ---
Pembro | 371 (58.2%) | 0.81 (0.71-0.93) | .0018
Chemo | 438 (68.8%) | |

Median (95% CI)
16.7 mo (13.9-19.7)
12.1 mo (11.3-13.3)

No. at Risk

<table>
<thead>
<tr>
<th>Months</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>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</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>
<tr>
<td>Chemo</td>
<td>637</td>
<td>485</td>
<td>316</td>
<td>166</td>
<td>88</td>
<td>24</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

OS: TPS ≥ 1%-49%

(Exploratory Analysis\(^a\))

**Events** | **HR (95% CI)**
--- | ---
Pembro | 214 (63.3%) | 0.92 (0.77-1.11)
Chemo | 239 (70.9%) | |

Median (95% CI)
13.4 mo (10.7-18.2)
12.1 mo (11.0-14.0)

*No alpha allocated to this comparison. Data cutoff date: February 26, 2018.
Please see full prescribing information for warnings, efficacy, risk, and safety.
OS: TPS ≥ 50%

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>157 (52.5%)</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>Chemo</td>
<td>199 (66.3%)</td>
<td></td>
</tr>
</tbody>
</table>

**Events**
Pembrolizumab

**HR (95% CI)**
0.69 (0.56-0.85)

**P**
.0003

**Median (95% CI)**
20.0 mo (15.4-24.9)
12.2 mo (10.4-14.2)

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Pembro</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>299</td>
<td>300</td>
</tr>
<tr>
<td>6</td>
<td>224</td>
<td>231</td>
</tr>
<tr>
<td>12</td>
<td>189</td>
<td>149</td>
</tr>
<tr>
<td>18</td>
<td>107</td>
<td>75</td>
</tr>
<tr>
<td>24</td>
<td>59</td>
<td>40</td>
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<td>30</td>
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<td>11</td>
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<tr>
<td>36</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data cutoff date: February 26, 2018.

Please see full prescribing information for warnings, efficacy, risk, and safety.

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**Summary**

- Carboplatin, paclitaxel, and pembrolizumab will become an option for patients with advanced NSCLC with squamous histology.
- Carboplatin, paclitaxel, bevacizumab, and atezolizumab will become an option for patients with advanced NSCLC with nonsquamous histology.
- Pembrolizumab was superior to chemotherapy for patients with PD-L1 ≥ 1%; my practice will be to use single-agent pembrolizumab in patients with PD-L1 ≥ 50%.
Contact Information

Call (toll-free) 866 858 7434
Email info@med-iq.com

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Thoracic Malignancies: Abbreviations and Acronyms

AE = adverse event
ALK = anaplastic lymphoma kinase
AUC = area under the curve
BICR = blinded independent central radiologic review
chemoRT = chemoradiation
CNS = central nervous system
CNS-RT = central nervous system radiation therapy
CP = carboplatin + paclitaxel
CPI = checkpoint inhibitor
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
EGFR = epidermal growth factor receptor
IA2 = second interim analysis
IHC = immunohistochemistry
ITT = intention to treat
IV = intravenous
KM = Kaplan Meier
NE = not estimable
NR = not reached
NSCLC = non–small cell lung cancer
ORR = objective response rate
OS = overall survival
PD = progressive disease
PD-L1 = programmed death-ligand 1
PFS = progression-free survival
PS = Performance Status
RT = radiation therapy
SBRT = stereotactic body radiotherapy
SCLC = small cell lung cancer
SRS = stereotactic radiosurgery
TPS = tumor proportion score
TSU = thoracic surgeons
VATS = video-assisted thoracoscopic surgery
WBRT = whole-brain radiation therapy
WT = wild type