Principles and Application of Immunotherapy for Cancer: Advanced NSCLC

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Faculty Disclosures

**Naiyer Rizvi, MD**, has disclosed that he has received consulting fees from AstraZeneca, Bristol-Myers Squibb, Merck, Novartis, and Roche.

**Marianne Davies, DNP, ACNP, AOCNP**, has disclosed that she has received consulting fees from Bristol-Myers Squibb and Genentech and fees for non-CME/CE services received directly from a commercial interest or their agents (e.g., speakers’ bureaus) from Genentech and Novartis.
Agenda

- Lung cancer and the immune system
  - Defining the role of the immune system in cancer
  - Tumor escape from immune surveillance
  - Harnessing the immune system as a treatment strategy for lung cancer

- Incorporating immunotherapeutic agents in lung cancer
  - Efficacy and safety of agents in development
  - Managing potential adverse events associated with immunotherapy
  - Educating pts about immunotherapy

- Selecting pts with lung cancer who may benefit from immunotherapy
T-Cell Response: First Signal

Class I MHC

Tumor

CD8+ T cell

Tumor antigen

Class II MHC

CD4+ T cell

Antigen-presenting cell

T-cell receptor

**T-Cell Response: Second Signal**

**Coactivation Signals**
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

**Inhibitory Signals**
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Use agonistic mAbs to ↑ activation
Use blocking mAbs to ↑ activation

Tumor Immunology: Overview

1. Dendritic cell
   - Tumor antigen
   - MHC
   - B7

2. Lymph node
   - Resting T cell
   - TCR
   - CD28

3. Activated T cell
   - T-cell clonal expansion
   - Perforin
   - Granzyme
   - Cytokines (IL-2)
Dampening the Immune System in Cancer

- Negative immune regulators
  - Inhibitory receptors
  - Suppressive cells
  - Suppressive enzymes (IDO, arginase)

PD-1 as a Target in Cancer Therapy

Activated T cell

Initial immune response

- Cytokines
- Proliferation
- Activation

CD28
CD80
CD86

Tumor or APC

Exhausted T cell

Persistent antigen stimulation

- CD28
- CD80
- CD86

MPDL3280A
MEDI4736
MSB0010718C

Nivolumab
Pembrolizumab
Pidilizumab

Incorporating Immunotherapeutic Agents in Lung Cancer
## Efficacy of Nivolumab Monotherapy in Pts With NSCLC

<table>
<thead>
<tr>
<th>Dose, mg/kg</th>
<th>ORR, % (n/N)</th>
<th>Median DOR, Mos (Range)</th>
<th>1-Yr PFS, % (95% CI)</th>
<th>2-Yr PFS, Mos (95% CI)</th>
<th>Median OS, Mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>17.1 (22/129)</td>
<td>17.0 (1.4+ to 36.8+)</td>
<td>22 (15-30)</td>
<td>9 (4-15)</td>
<td>9.9 (7.8-12.4)</td>
</tr>
<tr>
<td>1</td>
<td>3.0 (1/33)</td>
<td>14.7 (14.7 to 14.7)</td>
<td>19 (6-38)</td>
<td>0</td>
<td>9.2 (5.3-11.1)</td>
</tr>
<tr>
<td>3</td>
<td>24.3 (9/37)</td>
<td>17.0 (3.7+ to 32.6+)</td>
<td>30 (16-46)</td>
<td>11 (3-26)</td>
<td>14.9 (7.3-30.3)</td>
</tr>
<tr>
<td>10</td>
<td>20.3 (12/59)</td>
<td>19.1 (1.4+ to 36.8+)</td>
<td>19 (9-30)</td>
<td>10 (4-20)</td>
<td>9.2 (5.2-12.4)</td>
</tr>
</tbody>
</table>

- Durable responses: responses are ongoing in 41% of pts (9/22)
- Rapid responses: 50% of responding pts had response at first assessment (8 wks)
- 9/18 responders who discontinued for reasons other than disease progression responded for ≥ 9 mos (range: 9.2 – 16.4+ mos)
- 6 pts with unconventional “immune-related” responses were not included as responders

Nivolumab: Duration of Response and OS

**NSCLC Responders by Histology**

- **Squamous**
- **Nonsquamous**

**All Treated Subjects With NSCLC**
(n = 129)

- Died/Treated, n: 99/129
- Median, mos: 9.9
- 95% CI: 7.8 - 12.4

**Overall Survival (%)**

- 1 yr, 42%
- 2 yr, 24%
- 3 yr, 18%

CA209-063 (CheckMate-063): Phase II Study Design

- Stage IIIB/IV squamous NSCLC; ≥ 2 previous systemic therapies; ECOG PS 0-1 (N = 140)

- Planned to treat approximately 100 pts
  - Expected ORR of 10% to 50%, with 20% maximum width of exact 2-sided 95% CI

- Assessments (RECIST v1.1) performed at Wk 8 and every 6 wks

- Nivolumab 3 mg/kg IV Q2W (N = 117 treated)

- Treatment continues until progressive disease or unacceptable toxicity

- Primary endpoint: ORR and DOR by IRC (July 2014 database lock)

- Secondary endpoint: ORR and DOR by investigator (March 2014 database lock)

- Exploratory: safety and tolerability, PFS/OS, PD-L1 expression and efficacy

Response and Survival Status by Best Reduction in Target Lesion

CheckMate-017: Nivolumab vs Docetaxel in Previously Treated Squamous NSCLC

- Open-label, randomized phase III trial

Stage IIIB/IV squamous NSCLC; after failure of 1 previous platinum-based tx; ECOG PS 0-1 (N = 272)

- Primary endpoint: OS
- Secondary endpoint: ORR, PFS, associations with PD-L1 expression, QoL

Nivolumab
3 mg/kg IV q2w
(n = 135)

Docetaxel
75 mg/m² IV q3w
(n = 137)

CheckMate-017: Nivolumab vs Docetaxel

**Efficacy**

- **Median OS, Mos (95% CI):**
  - Nivolumab: 9.2 (7.3-13.3)
  - Docetaxel: 6.0 (5.1-7.3)
- **1-Yr OS, Mos (95% CI):**
  - Nivolumab: 42 (34-50)
  - Docetaxel: 24 (17-31)
- HR: 0.59 (95% CI: 0.44-0.79); \( P < .001 \)

CheckMate-017: Nivolumab vs Docetaxel

Efficacy

Nivolumab was FDA approved in metastatic squamous NSCLC on or after progression with platinum-based chemotherapy based on data from CheckMate-063 and -017.

CheckMate 057: Nivo vs Docetaxel in Previously Treated Nonsquamous NSCLC

Stratified by previous maintenance therapy (yes vs no) and line of therapy (second vs third line)

Pts with stage IIIB/IV nonsquamous NSCLC and ECOG PS 0-1 who failed 1 prior platinum doublet chemotherapy ± TKI therapy (N = 582)

- **Nivolumab 3 mg/kg IV q2w**
  - (n = 292)

- **Docetaxel 75 mg/m² IV q3w**
  - (n = 290)

Primary endpoint: OS
Secondary endpoints: ORR, PFS, efficacy by PD-L1 expression, safety, QoL

CheckMate 057: Increased Efficacy of Nivo vs Docetaxel in Nonsquamous NSCLC

**Overall Survival**

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>Median OS Nivolumab, mos</th>
<th>Median OS Docetaxel, mos</th>
<th>Unstratified HR (95% CI)</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1%</td>
<td>17.2</td>
<td>9.0</td>
<td>0.59 (0.43-0.82)</td>
<td>.0646</td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>10.4</td>
<td>10.1</td>
<td>0.90 (0.66-1.24)</td>
<td></td>
</tr>
<tr>
<td>≥ 5%</td>
<td>18.2</td>
<td>8.1</td>
<td>0.43 (0.30-0.63)</td>
<td>.0004</td>
</tr>
<tr>
<td>&lt; 5%</td>
<td>9.7</td>
<td>10.1</td>
<td>1.01 (0.77-1.34)</td>
<td></td>
</tr>
<tr>
<td>≥ 10%</td>
<td>19.4</td>
<td>8.0</td>
<td>0.40 (0.26-0.59)</td>
<td>.0002</td>
</tr>
<tr>
<td>&lt; 10%</td>
<td>9.9</td>
<td>10.3</td>
<td>1.00 (0.76-1.31)</td>
<td></td>
</tr>
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</table>

**Median OS, mos**

<table>
<thead>
<tr>
<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 292)</th>
</tr>
</thead>
</table>
| 12.2                | 9.4                 | Median OS: 12.2 mos vs 9.4 mos; HR: 0.73 (95% CI: 0.59, 0.89); P = .0015

CheckMate 057: Increased Efficacy of Nivo vs Docetaxel in Nonsquamous NSCLC

The FDA expanded the approval of nivolumab to include patients with non-squamous NSCLC on or after progression with platinum-based chemotherapy with the data from CheckMate-057.

<table>
<thead>
<tr>
<th>PD-L1 Expression Level</th>
<th>Median OS Nivolumab, mos</th>
<th>Median OS Docetaxel, mos</th>
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KEYNOTE-001: Subanalysis of Phase I Pembrolizumab Trial in NSCLC

Mandatory tumor biopsy

Treatment-naive or previously treated advanced NSCLC (N = 495)

- Administered tumor assessment: imaging every 9 wks
  - Primary: RECIST v.1.1 (independent central review)
  - Secondary: immune-related response criteria (irRC; investigator assessed)

- Tumor biopsy

  - Tumor biopsy within 60 days prior to first dose of pembrolizumab required
  - Tumor PD-L1 expression determined by prototype assay to inform enrollment; Samples were independently reanalyzed using clinical trial IHC assay

Keynote-001: Pembrolizumab Efficacy in Overall Population

<table>
<thead>
<tr>
<th>ORR by RECIST, % (95% CI)</th>
<th>N</th>
<th>All Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>495</td>
<td>19.4 (16.0-23.2)</td>
</tr>
<tr>
<td>▪ Treatment naive</td>
<td>101</td>
<td>24.8 (16.7-34.4)</td>
</tr>
<tr>
<td>▪ Previously treated</td>
<td>394</td>
<td>18.0 (14.4-22.2)</td>
</tr>
<tr>
<td>▪ Nonsquamous</td>
<td>401</td>
<td>18.7 (15.0-22.9)</td>
</tr>
<tr>
<td>▪ Squamous</td>
<td>85</td>
<td>23.5 (15.0-34.0)</td>
</tr>
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</table>

**PD-L1 NSCLC Sample IHC Staining**

- PD-L1 = 0% positive
  - Negative

- PD-L1 = 2% positive
  - Weak positive
  - (1% to 49%)

- PD-L1 = 100% positive
  - Strong positive
  - (50% to 100%)

Keynote-001: Pembrolizumab Efficacy by PD-L1 Expression

<table>
<thead>
<tr>
<th>Percent PD-L1 staining</th>
<th>N</th>
<th>All Cohorts</th>
</tr>
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<tbody>
<tr>
<td>≥ 50%</td>
<td>73</td>
<td>45.2 (33.5-57.3)</td>
</tr>
<tr>
<td>1% - 49%</td>
<td>103</td>
<td>16.5 (9.9-25.1)</td>
</tr>
<tr>
<td>&lt; 1%</td>
<td>28</td>
<td>10.7 (2.3-28.2)</td>
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</table>

PFS and OS survival curves:
- PS ≥ 50% (n = 119)
- PS < 1% (n = 76)
- PS 1 - 49% (n = 161)

Proportion score for 356 pts in training, validation groups with slides sectioned ≤ 6 months of staining
Keynote-001: Pembrolizumab Efficacy by PD-L1 Expression

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</table>

Pembrolizumab was FDA approved in metastatic NSCLC expressing PD-L1, as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy based on data from KEYNOTE-001.

Managing Potential Adverse Events Associated With Immunotherapy
Summary of PD-1/PD-L1 Blockade Immune-Mediated Toxicities

**Occasional (5% to 20%)**

- Fatigue
- Rash: maculopapular and pruritus
  - Topical treatments
- **Diarrhea/colicitis**
  - Initiate steroids early, taper slowly
- Hepatitis/liver enzyme abnormalities

**Infrequent (< 5%)**

- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis
- Pneumonitis
- Grade 3/4 toxicities uncommon

Immune Adverse Events

- **Onset:**
  - Average is 6-12 wks after initiation of therapy
  - Can occur within days of the first dose, after several mos of treatment, and after discontinuation of therapy

- Pt complaints are autoimmune and drug related until proven otherwise
  - Rule out infections, metabolic causes, tumor effects, etc

- Early recognition, evaluation, and treatment are critical
**PD-1/PD-L1 Inhibition: Managing for Treatment-Related Adverse Events**

Any grade 1 AE or Isolated hypothyroidism

Symptom management or replacement therapy for hypothyroidism

Continue PD-1 tx and monitor

Grade 2 pneumonitis, nephritis, colitis, hepatitis
Symptomatic hypophysitis

Any grade 3 AE

Hold PD-1 tx and administer steroids
After improvement to ≤ grade 1, taper steroids over at least 1 mo

Resume if:
AE remains at grade 0/1 after steroid taper

Permanently discontinue if:
- No improvement to ≤ grade 1 within 12 wks
- Cannot taper steroids to ≤ 10 mg/day of prednisone or equivalent within 12 wks

Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide.
PD-1/PD-L1 Inhibition: Managing for Treatment-Related Adverse Events

Grade 3/4 pneumonitis
Grade 3/4 nephritis
Grade 3/4 infusion-related reaction
Any life-threatening or grade 4 AE
Any severe or grade 3 recurrent AE

Hepatitis associated with
- AST/ALT > 5 x ULN
- AST/ALT ≥ 50% ↑ from baseline lasting ≥ 1 wk*
- Total bilirubin > 3 x ULN

*In pts with liver metastasis who begin treatment with grade 2 elevation of AST/ALT.

Initiate steroid therapy
Permanently discontinue PD-1 tx

Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide.
Key to Optimal Pt Management

- All members of the healthcare team should be educated about potential AEs
- Rapid and timely diagnostic and therapeutic intervention is imperative for optimal control of irAEs
  - Persistent grade 2 irAEs and grade 3/4 irAEs are treated with steroids
  - Early discontinuation of steroids may predispose to relapse
- Reinitiation of treatment may be possible with optimal management
- Approximately 5% to 10% of patients experience evidence of enlarging tumor lesions prior to a response
  - Pseudoprogression can be managed by continuing treatment and monitoring closely

Optimal management is attainable through continued communication between all members of the healthcare team and individual patients
Pt Education on Novel Therapies

- Pt education should include information on:
  - Adverse reaction profiles that differ from standard chemotherapy
  - Early recognition of irAEs essential for effective treatment
  - irAEs are infrequent, treatable and respond well to steroids
  - Who and when to call for adverse reactions

- Reinforce teaching points at every point of contact, office and treatment visits, and phone contact
  - Notify your healthcare team if you are admitted to another hospital
Pt and Family Education

- Assess for both pt and caregiver
  - Knowledge of therapy and the disease process
  - Educational level and preferred learning methods

- Provide information on:
  - Administration schedule of therapy
  - Time to response
    - Time required to mount antitumor response
  - Tumor assessment
    - May demonstrate early progression or new lesions, prior to demonstrating response
Future Directions for Immunotherapy in NSCLC
Phase II POPLAR Trial: Atezolizumab vs Docetaxel in Previously Treated NSCLC

- Primary endpoint: OS in PD-L1–selected and ITT populations
- Secondary endpoints: overall safety as well as PFS, ORR, DoR in PD-L1–selected and ITT populations

Stratified by PD-L1 immune cell expression (0 vs 1 vs 2 vs 3), histology (squamous vs nonsquamous), and line of therapy (second vs third line)

Pts with locally advanced or metastatic NSCLC and ECOG PS 0-1 who failed prior platinum-containing chemotherapy (N = 287)

- Atezolizumab 1200 mg IV q3w (n = 144)
- Docetaxel 75 mg/m² IV q3w (n = 143)

POPLAR: Efficacy of Atezolizumab Increased With Higher PD-L1 Expression

<table>
<thead>
<tr>
<th>Interim Median OS Outcomes</th>
<th>Atezolizumab (n = 144)</th>
<th>Docetaxel (n = 143)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT population (N = 287)</td>
<td>11.4</td>
<td>9.5</td>
<td>0.77 (0.55-1.06)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Subgroups based on PD-L1 expression*
- TC0 and IC0 (n = 92) 9.7 9.7 1.12 (0.64-1.93) .70
- TC1/2/3 or IC1/2/3 (n = 195) NR 9.1 0.63 (0.42-0.94) .024
- TC2/3 or IC2/3 (n = 105) 13.0 7.4 0.56 (0.33-0.94) .026
- TC3 or IC3 (n = 47) NR 11.1 0.46 (0.19-1.09) .070

*PD-L1 expression measured by SP142 IHC assay (low expression – TC0/IC0, high expression - TC3/IC3).

- PFS and ORR: similar trends in outcome for atezolizumab vs docetaxel based on PD-L1 expression
  - Median PFS in ITT population: 2.8 vs 3.4 mos (HR: 0.98)
  - Median PFS in TC3 or IC3 population: 7.8 vs 3.9 mos (HR: 0.57)
  - ORR in ITT population: 15% vs 15%
  - ORR in TC3 or IC3 population: 38% vs 13%
- Interim data based on minimum of 10 mos of follow-up

Activity of Atezolizumab by Immune Cell or Tumor PD-L1 Expression

- Specimens scored by % of cells PD-L1+ per area:
  - IHC 0: < 1%
  - IHC 1: 1% to < 5%
  - IHC 2: 5% to < 10%
  - IHC 3: ≥ 10%

Best response: CR or PR
Best response: SD

## Activity of Atezolizumab by Immune Cell PD-L1 IHC

<table>
<thead>
<tr>
<th>Diagnostic Population</th>
<th>IHC 3 (n = 6)</th>
<th>IHC 2 (n = 7)</th>
<th>IHC 1 (n = 13)</th>
<th>IHC 0 (n = 20)</th>
<th>Unknown (n = 7)</th>
<th>All Pts (N = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (RECIST), n (%)</td>
<td>5 (83)</td>
<td>1 (14)</td>
<td>2 (15)</td>
<td>4 (20)</td>
<td>0</td>
<td>12 (23)</td>
</tr>
<tr>
<td>SD (best response), n (%)</td>
<td>0</td>
<td>3 (43)</td>
<td>3 (23)</td>
<td>7 (35)</td>
<td>5 (71)</td>
<td>18 (34)</td>
</tr>
<tr>
<td>SD ≥ 24 wks, n (%)</td>
<td>0</td>
<td>0</td>
<td>1 (8)</td>
<td>4 (20)</td>
<td>4 (57)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>PD (best response), n (%)</td>
<td>1 (17)</td>
<td>2 (29)</td>
<td>7 (54)</td>
<td>9 (45)</td>
<td>2 (29)</td>
<td>21 (40)</td>
</tr>
<tr>
<td>24-wk PFS, %</td>
<td>83.3</td>
<td>14.3</td>
<td>25.6</td>
<td>45.0</td>
<td>71.4</td>
<td>44.7</td>
</tr>
<tr>
<td>Median PFS, wks (95% CI)</td>
<td>NE (5-NE)</td>
<td>11 (1-17)</td>
<td>6 (5-43)</td>
<td>13 (6-37)</td>
<td>NE (6-NE)</td>
<td>15 (6-43)</td>
</tr>
</tbody>
</table>

Phase III OAK Trial: Atezolizumab vs Docetaxel in Previously Treated NSCLC

Stratified by tumor PD-L1 status (IHC), prior chemo regimens (1 vs 2), and histology (nonsquamous vs squamous)

Stage IIIB/IV or recurrent NSCLC; 1-2 prior regimens, including 1 previous platinum-based treatment
(estimated N = 1100)

- Primary endpoint: OS
- Secondary endpoint: ORR, PFS, DoR, Safety

Atezolizumab
1200 mg IV q3w

Docetaxel
75 mg/m² IV q3w

ClinicalTrials.gov. NCT02008227.
## Recent Early Phase Trials in NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Population</th>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
</table>
| Durvalumab (Anti-PD-L1) | Squamous (n = 88) | ORR: 16%  
27% in PD-L1+  
5% in PD-L1-  
Squamous: 21%  
Nonsquamous: 13% | Tx-related AEs:  
Any: 50% of pts  
Grade 3/4: 8%  
Leading to d/c: 5%  
No tx-related colitis or hyperglycemia, no grade 3/4 pneumonitis |
| Durvalumab + tremelimumab (Anti-CTLA-4) | Advanced NSCLC (n = 102) | ORR: 27%  
33% PD-L1+  
27% PD-L1- | Tx-related AEs:  
Any: 63%-89% of pts by cohort  
Grade 3/4: 29%-78% by cohort  
Leading to d/c: 7%-44% by cohort  
Grade 3/4 immune-related AEs: colitis (9%), pneumonitis (4%), and hypothyroidism (1%) |
| Pembrolizumab + ipilimumab (KEYNOTE-021) | Recurrent NSCLC after ≤ 2 regimens (n = 18) | ORR: 39% | Tx-related AEs:  
Any: 83% of pts  
Grade 3/4: 17% (adrenal insufficiency, maculopapular rash, drug eruption)  
Leading to d/c: 11% |

Phase III Trials: Durvalumab ± Tremelimumab vs SoC in Advanced NSCLC

- Randomized, open-label, multi-center, global phase III trials: NEPTUNE\(^1\) and MYSTIC\(^2\)

- Advanced, metastatic NSCLC; EGFR and ALK WT; no prior therapy for advanced disease

- Primary endpoint: PFS, OS

- Secondary endpoint: ORR, PFS, DoR, Safety

A Roadmap of Immunotherapy-Tumor Interactions

1. **Release of cancer cell antigens**
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. **Cancer antigen presentation**
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. **Priming and activation**
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. ** Trafficking of T cells to tumors**

5. **Infiltration of T cells into tumors**
   - Anti-VEGF

6. **Recognition of cancer cells by T cells**
   - CARs

7. **Killing of cancer cells**
   - Anti–PD-L1
   - Anti–PD-1
   - IDO inhibitors

Conclusions

- Immunotherapy for lung cancer can induce durable responses and can result in prolonged OS
- Different patterns of response with checkpoint inhibition require ongoing education for pts
- Immune-related adverse events are a unique spectrum of adverse events with checkpoint inhibition that require learning new ways to manage toxicity
- Improved understanding of the immune system and ongoing clinical trials with immunotherapy will likely result in an ongoing evolution in treatment for pts with NSCLC
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