Advances in Cancer Immunotherapy for Solid Tumors

*Expert Perspectives on The New Data*

**Moderator**

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Los Angeles, CA
Learning Objectives

1) Describe the basic principles of tumor immunology and the mechanisms of action of current and emerging cancer immunotherapies used in solid tumors.

2) Evaluate the latest clinical trial data regarding emerging cancer immunotherapies in HNSCC, NSCLC, mesothelioma, gastric cancer, melanoma, and other solid tumors, including the use of both monotherapy and combination regimens.

Learning Objectives (cont.)

3) Explore the role of biomarkers in patient selection to improve targeted use of immune checkpoint inhibitors.

4) Identify practical strategies for using current and emerging cancer immunotherapies, including prevention, early detection, and management of immune-related adverse effects.
New Era in Cancer Therapy
Harnessing The Immune System

Immune Checkpoint Blockade
CTLA-4 and PD-1/PD-L1 Inhibitors
T-Cell Targets
Activating and Inhibitory Co-Receptors

Activating Receptors
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory Receptors
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Agonistic antibodies

Blocking antibodies

T-cell stimulation

Boosting Antitumor Immunity
Targeting Four Nodes

- Block immune suppression
- Induce immunogenic cancer-cell death
- Enhance antigen presenting cell function/adjuvanticity
- Enhance T cell/macrophage effector activity

Immune Checkpoint Blockade

Unique Clinical Features

Tumor Response Kinetics

• Immune-mediated response patterns may differ from those associated with conventional therapies, which has prompted the development of immune-related response criteria (irRC)\(^a\)

Immune-Related Adverse Events (irAEs)

• By enhancing immune system function, immune checkpoint blockade can lead to autoinflammatory side effects called irAEs\(^b\)


HNSCC

Two Distinct Diseases

Carcinogen

Viral

\[\text{Carcinogen:} \quad \text{p53 mut} \rightarrow \text{p16} \rightarrow 3p, 4q, 5q, 8p, 13q del\]

\[\text{Viral:} \quad \text{pRB} \rightarrow \text{E7} \rightarrow \text{E6} \rightarrow \text{p53} \rightarrow \text{HPV}\]
HPV+ Tumor Microenvironment

*Enriched for PD-1+ CD8+ T cells*

- PD-1 is an immune checkpoint receptor expressed by tumor infiltrating lymphocytes, limiting the function of activated T cells
- PD-L1 protein expression is higher in HPV+ tumors
  - 70% of HPV+ specimens were found to have PD-L1 expression compared to 43.3% of the HPV- specimens

KEYNOTE-012

*Expansion Cohort*

<table>
<thead>
<tr>
<th>Best overall response</th>
<th>Total N=117</th>
<th>HPV+ N=34</th>
<th>HPV- N=81</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>95% CI</td>
<td>N (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29 (24.8)</td>
<td>17.3-33.6</td>
<td>7 (20.6)</td>
<td>8.7-37.9</td>
</tr>
<tr>
<td>Complete Response</td>
<td>1 (0.9)</td>
<td>0.0-4.7</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>28 (23.9)</td>
<td>16.5-32.7</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>29 (24.8)</td>
<td>17.3-33.6</td>
<td>9 (26.5)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>48 (41.0)</td>
<td>32.0-50.5</td>
<td>13 (38.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=132 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior lines of therapy for recurrent/metastatic disease</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (16.7)</td>
</tr>
<tr>
<td>1</td>
<td>30 (22.7)</td>
</tr>
<tr>
<td>2 or more</td>
<td>78 (59.1)</td>
</tr>
</tbody>
</table>

CheckMate 141
Study Design
Randomized, Global, Phase 3 trial of the efficacy and safety of nivolumab versus investigator’s choice in patients with R/M HNSCC

Key Eligibility Criteria
- R/M HNSCC of the oral cavity, oropharynx, larynx, or hypopharynx
- ECOG PS 0–1
- Not amenable to curative therapy
- Progression on or within 6 months of last dose of platinum-based therapy
- Documentation of p16 to determine HPV status
- No active CNS metastases

Stratification factor
- Prior cetuximab treatment

Randomized
361/361

Nivolumab
3mg/kg IV Q2W

Investigator’s Choice
- Methotrexate 40-60 mg/m² IV weekly
- Docetaxel 30-40 mg/m² IV weekly
- Cetuximab 400mg/m² IV once, then 250mg/m² weekly

Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life


CheckMate 141
Overall Survival

### CheckMate 141
**OS by p16 Status**

<table>
<thead>
<tr>
<th>p16+</th>
<th></th>
<th>p16–</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment Arm</strong></td>
<td><strong>Median OS, mo (95% CI)</strong></td>
<td><strong>HR (95% CI)</strong></td>
<td><strong>Treatment Arm</strong></td>
</tr>
<tr>
<td>Nivolumab (n=63)</td>
<td>9.1 (7.2-10.0)</td>
<td>0.56 (0.32-0.99)</td>
<td>Nivolumab (n=50)</td>
</tr>
<tr>
<td>Investigator’s Choice (n=29)</td>
<td>4.4 (3.0–9.8)</td>
<td></td>
<td>Investigator’s Choice (n=36)</td>
</tr>
</tbody>
</table>


### Durvalumab and/or Tremelimumab
**Trials in HNSCC**

#### Setting
- **Phase II HAWK**
  - 2L HNSCC post plat in R/M setting
- **Phase II CONDOR**
  - 2L HNSCC post plat in R/M setting
- **Phase III EAGLE**
  - 2L HNSCC post plat
  - 1L pts who progressed within 6 mo of multi-modal tx w/pt in the locally advanced setting

#### Regimen
- Durvalumab
- Durvalumab + Tremelimumab
- Durvalumab
- Durvalumab + Tremelimumab
- Durvalumab
- SOC

#### PD-L1 status
- + N=112
- N=120
- N=60
- N=60
- + N=100
- N=140
- + N=100
- N=Adaptive 140
- + N=100
- N=140

Clinical Trial Identifiers: NCT02207530, NCT02319044, NCT02369874
Other Solid Tumors
Select Trials

- CheckMate 032: Advanced/metastatic GC/GEC
- CheckMate 025: Kidney cancer
- KEYNOTE-028: Advanced esophageal carcinoma
- KEYNOTE-012: Advanced GC, TNBC
- NCT02516241; NCT02256436; NCT02302807: Bladder cancer
- NCT02267603: Advanced Merkel-cell carcinoma
- NCT01876511: MMR-deficient cancers

ICIs in NSCLC and Mesothelioma
Current Status

- Nivolumab and pembrolizumab are approved for use as 2nd line therapy of NSCLC.
- Atezolizumab shows improved activity over docetaxel in the 2nd line treatment of NSCLC.
- Combination therapy with PD-1/PD-L1 shows promise in NSCLC.
- PD-1/PD-L1 pathway blockade is active in mesothelioma.
CheckMate 017
OS and PFS by PD-L1 Expression

Survival benefit with nivolumab was independent of PD-L1 expression level

<table>
<thead>
<tr>
<th>PD-L1 expression</th>
<th>Patients, N</th>
<th>Unstratified HR (95% CI)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1%</td>
<td>63</td>
<td>0.69 (0.45, 1.05)</td>
<td>.56</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>54</td>
<td>0.58 (0.37, 0.92)</td>
<td>.47</td>
</tr>
<tr>
<td>≥5%</td>
<td>42</td>
<td>0.53 (0.31, 0.89)</td>
<td>.41</td>
</tr>
<tr>
<td>&lt;5%</td>
<td>75</td>
<td>0.70 (0.47, 1.02)</td>
<td></td>
</tr>
<tr>
<td>≥10%</td>
<td>36</td>
<td>0.50 (0.28, 0.89)</td>
<td></td>
</tr>
<tr>
<td>&lt;10%</td>
<td>81</td>
<td>0.70 (0.48, 1.01)</td>
<td></td>
</tr>
<tr>
<td>Not quantifiable</td>
<td>18</td>
<td>0.39 (0.19, 0.82)</td>
<td></td>
</tr>
</tbody>
</table>

| PFS               |             |                          |                   |
| ≥1%              | 63          | 0.67 (0.44, 1.01)         | .70               |
| <1%              | 54          | 0.66 (0.43, 1.00)         |                   |
| ≥5%              | 42          | 0.54 (0.32, 0.90)         | .16               |
| <5%              | 75          | 0.75 (0.52, 1.08)         |                   |
| ≥10%             | 36          | 0.58 (0.33, 1.02)         | .35               |
| <10%             | 81          | 0.70 (0.49, 0.99)         |                   |
| Not quantifiable | 18          | 0.45 (0.23, 0.89)         |                   |

PD-L1 expression was measured in pre-treatment tumor biopsies (DAKO automated IHC assay)


KEYNOTE-010
OS and PFS by PD-L1 Expression

Durvalumab + Tremelimumab
Phase Ib Study

Activity

<table>
<thead>
<tr>
<th></th>
<th>All evaluable</th>
<th>PD-L1+ ≥25%</th>
<th>PD-L1&lt;25%</th>
<th>PD-L1&lt;0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>6/26 (23%)</td>
<td>2/9 (22%)</td>
<td>4/14 (29%)</td>
<td>4/10 (40%)</td>
</tr>
<tr>
<td>DCR</td>
<td>9/26 (35%)</td>
<td>3/9 (33%)</td>
<td>6/14 (43%)</td>
<td>4/10 (50%)</td>
</tr>
</tbody>
</table>

Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Diarrhea</th>
<th>Pruritus</th>
<th>Rash</th>
<th>↑ Amylase</th>
<th>↑ ALT</th>
<th>Hypothyroidism</th>
<th>Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2</td>
<td>16%</td>
<td>20%</td>
<td>11%</td>
<td>14%</td>
<td>7%</td>
<td>7%</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>7%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2%</td>
<td>2%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Durvalumab (10-20 mg/kg q 2-4 weeks) plus Tremelimumab 1 mg/kg
All evaluable pts with >24 weeks of follow-up
ORR – Objective responses confirmed
DCR – Confirmed response and stable disease >24 weeks
Response rate and DCR


CheckMate 012
Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (N=38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (N=39)</th>
<th>Nivo 3 Q2W (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>47 (31, 64)</td>
<td>39 (23, 55)</td>
<td>23 (13, 37)</td>
</tr>
<tr>
<td>Best overall response, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Partial response</td>
<td>47</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>Stable disease</td>
<td>32</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>13</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>8</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>8.1 (5.6, 13.6)</td>
<td>3.9 (2.6, 13.2)</td>
<td>3.6 (2.3, 6.6)</td>
</tr>
<tr>
<td>1-year OS, mos (95% CI)</td>
<td>NR</td>
<td>69 (52, 81)</td>
<td>73 (59, 83)</td>
</tr>
<tr>
<td>Median length of follow-up, mos (range)</td>
<td>12.9 (0.9–18.0)</td>
<td>11.8 (1.1–18.2)</td>
<td>14.3 (0.2–30.1)</td>
</tr>
</tbody>
</table>

• Median DOR was not reached in any arm
• Unconventional immune-related responses were observed in arms Nivo 3 Q2W + Ipi 1 Q12W (N=2), Nivo 3 Q2W + Ipi 1 Q6W (N=1) and Nivo 3 Q2W (N=3)

CheckMate 012
Safety

<table>
<thead>
<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W (N=38)</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W (N=39)</th>
<th>Nivo 3 Q2W (N=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AEs, %</td>
<td>Any Grade 82 Grade 3–4 37</td>
<td>Any Grade 72 Grade 3–4 33</td>
<td>Any Grade 71 Grade 3–4 19</td>
</tr>
<tr>
<td>Treatment-related AEs leading to discontinuation, %</td>
<td>11 5</td>
<td>13 8</td>
<td>10 10</td>
</tr>
</tbody>
</table>

There were no treatment-related deaths

PD-1/PD-L1 + CTLA-4 Blockade
Efficacy by PD-L1 Expression

<table>
<thead>
<tr>
<th></th>
<th>Nivo 3 Q2W + Ipi 1 Q12W</th>
<th>Nivo 3 Q2W + Ipi 1 Q6W</th>
<th>Nivo 3 Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (n/N)</td>
<td>30 (3/10)</td>
<td>0 (0/7)</td>
<td>14 (2/14)</td>
</tr>
<tr>
<td>&lt;1% PD-L1</td>
<td>57 (12/21)</td>
<td>57 (13/23)</td>
<td>28 (9/32)</td>
</tr>
<tr>
<td>≥1% PD-L1</td>
<td>100 (6/6)</td>
<td>86 (6/7)</td>
<td>50 (6/12)</td>
</tr>
<tr>
<td>≥50% PD-L1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>4.7 (0.9, NR)</td>
<td>2.4 (1.7, 2.9)</td>
<td>6.6 (2.0, 11.2)</td>
</tr>
<tr>
<td>&lt;1% PD-L1</td>
<td>8.1 (5.6, NR)</td>
<td>10.6 (3.6, NR)</td>
<td>3.5 (2.2, 6.6)</td>
</tr>
<tr>
<td>≥1% PD-L1</td>
<td>13.6 (6.4, NR)</td>
<td>NR (7.8, NR)</td>
<td>8.4 (2.2, NR)</td>
</tr>
<tr>
<td>≥50% PD-L1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year OS, mos (95% CI)</td>
<td>NC (66, 97)</td>
<td>NC (83, 60, 93)</td>
<td>79 (47, 93)</td>
</tr>
<tr>
<td>&lt;1% PD-L1</td>
<td>90 (66, 97)</td>
<td>100 (100, 100)</td>
<td>69 (50, 82)</td>
</tr>
<tr>
<td>≥1% PD-L1</td>
<td></td>
<td></td>
<td>83 (48, 96)</td>
</tr>
<tr>
<td>≥50% PD-L1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Durvalumab (10–20 mg/kg Q2W or Q4W) plus tremelimumab (1 mg/kg)

<table>
<thead>
<tr>
<th></th>
<th>All evaluable</th>
<th>PD-L1+ ≥25%</th>
<th>PD-L1– &lt;25%</th>
<th>PD-L1– 0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>6/26 (23%)</td>
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<td>6/14 (43%)</td>
<td>4/10 (50%)</td>
</tr>
</tbody>
</table>

CheckMate 012
Efficacy by Smoking and EGFR Status


PD-1/PD-L1 Blockade
Frontline Setting

KEYNOTE-001

Tremelimumab in Mesothelioma

2nd and 3rd Line Treatment Setting

### Phase III Study

<table>
<thead>
<tr>
<th></th>
<th>Tremelimumab 10 mg/kg every 4 weeks x 7 doses then every 12 weeks</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>382</td>
<td>189</td>
</tr>
<tr>
<td>Median OS</td>
<td>7.7 mo</td>
<td>7.3 mo</td>
</tr>
<tr>
<td>HR=0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 or &gt; Rx related AE</td>
<td>65%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Failed to meet Primary Endpoint of OS

Phase 2 study of Tremelimumab + Durvalumab is ongoing (NCT02588131)


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**PARP + PD-1/PD-L1 Inhibition**

*Potential Combination?*
## Immune Checkpoints in Melanoma Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Control Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribas 2013</td>
<td>Tremelimumab</td>
<td>Temozolomide or dacarbazine</td>
</tr>
<tr>
<td>Hodi 2010</td>
<td>Ipilimumab +/- gp100</td>
<td>gp100</td>
</tr>
<tr>
<td>Robert 2011</td>
<td>Ipilimumab + dacarbazine</td>
<td>Dacarbazine + placebo</td>
</tr>
<tr>
<td>Weber 2015</td>
<td>Nivolumab</td>
<td>Dacarbazine or paclitaxel + carboplatin</td>
</tr>
<tr>
<td>Ribas 2015</td>
<td>Pembrolizumab</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Robert 2015</td>
<td>Nivolumab</td>
<td>Dacarbazine</td>
</tr>
</tbody>
</table>


## Nivolumab Phase I Trial Follow-up

### Overall Survival at 5 Years

- **All Patients (events: 69/107), median and 95% CI:** 17.3 (12.5–37.8)
- **NIVO 3 mg/kg (events: 11/17), median and 95% CI:** 20.3 (7.2–NR)

Hodi FS, et al. AACR. 2016. (Abstract CT001)
Pembrolizumab Phase Ib Trial Follow-up
*Overall Survival at 3 Years*

<table>
<thead>
<tr>
<th>Patients (N)</th>
<th>Events (n)</th>
<th>Median (95% CI)</th>
<th>Survival Rate at 36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>655</td>
<td>358 (55%)</td>
<td>24.4 months (20.2-29.0)</td>
<td>40%</td>
</tr>
</tbody>
</table>


---

**Cancer Immunotherapy**

*Future Advances and Developments*

- Generate T cells:
  - + Anti-CTLA4
  - + Immune-activating antibodies or cytokines
  - + TLR agonists or oncolytic viruses
  - + IDO or macrophage inhibitors
  - + Targeted therapies

- Bring T cells into tumors:
  - + Vaccines
  - + TCR engineered ACT
  - + CAR engineered ACT

Optimal duration of PD-1/PD-L1 blockade remains to be determined.
Key Take Home Points

• The advent of immunotherapy represents a new era for patients with HNSCC, particularly those with the platinum-refractory disease.
  - The future goals and opportunities include building various immunotherapy-based combination therapies, and clearly identifying subgroups of patients likely to respond to them.

• For patients with lung cancer, immunotherapy is now here to stay, and we hope to bring it from the second-line up to the first-line treatment setting.

• In melanoma, we have made a lot progress and actually now even talk about a potential cure with the patients.
  - Now we have to step back and learn from the things that worked, why they worked, why others did not work, and what we will have to do differently in the future.

Thank you for participating in this activity.
**irAEs**

**General Issues**

- Infections and other etiologies should be ruled out or deemed unlikely as contributing to the irAEs

- Most irAEs occur during the first 3-4 months
  - Late irAEs, however, also can occur (e.g., one episode has been seen at month 47 during maintenance phase of therapy)
  - Each irAE has different kinetics of onset and some can wax and wane, particularly colitis

- Corticosteroids can be used to manage almost all irAEs
  - Prolonged steroid tapers are required


**Management of irAEs**

**General Principles**

- Responsibility of all health care providers

- *Early reporting by patients with close monitoring, and early intervention by health care providers*

- Provide thorough and continuous patient education about the signs and symptoms of irAEs

- Assess for signs and symptoms of irAEs before each cycle of immunotherapy

- Know management algorithm specific to each irAE
  - Safety profiles of immunosuppressants

- Monitor and manage toxicities of immunosuppressants
  - Hyperglycemia and diabetes
  - Opportunistic infection
Abbreviations

- AE = Adverse event
- CNS = Central nervous system
- DOR = Duration of response
- ECOG PS = Eastern Cooperative Oncology Group performance status
- GC = Gastric cancer
- GEC = Gastroesophageal junction cancer
- HNSCC = Head and neck squamous cell carcinoma
- HPV = Human papillomavirus
- HR = Hazard ratio
- ICI = Immune checkpoint inhibitors
- irRC = Immune-related response criteria
- NSCLC = Non-small cell lung cancer
- OS = Overall survival
- ORR = Objective response rate
- PD-1 = Programmed death 1
- PD-L1 = Programmed death ligand 1
- PFS = Progression-free survival
- R = Randomized
- R/M = Recurrent/metastatic
- TNBC = Triple-negative breast cancer