The Immune Checkpoint Inhibitor Landscape
Where We Are in 2019
This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Bristol-Myers Squibb.
Dr. Adams is an associate professor, Department of Pharmacy Practice and Science, in the College of Pharmacy at the University of Kentucky. He serves as graduate faculty, director of the hematology/oncology residency program, and member of the Markey Cancer Center, where he has a clinical practice site. Dr. Adams received his BS in Pharmacy from the University of Utah and his PharmD from the University of Texas at Austin. He completed a residency in hematology/oncology at the Audie L. Murphy Memorial VA Hospital in San Antonio and a 2-year fellowship in immunology and transplantation at the University of Florida.
Dr. Brenner is a clinical pharmacy specialist in hematology/oncology and is the PGY2 oncology research coordinator at UPMC Hillman Cancer Center and UPMC Presbyterian Shadyside Hospital. He received his PharmD from the University of Michigan, and he completed his PGY1 and PGY2 in oncology at the University of Kentucky. He completed a research fellowship at St. Jude Children's Research Hospital before entering academia at the University of Arizona as clinical oncology faculty. In 2007, Dr. Brenner moved from Tucson to Pittsburgh, where he now practices in all aspects of clinical hematology/oncology practice. He has been a board-certified oncology pharmacist since 2009.
Panelist

Lisa Davis, PharmD, FCCP, BCPS, BCOP

Professor, Pharmacy Practice and Science
University of Arizona College of Pharmacy
Oncology Clinical Pharmacist
Banner University Medical Center
Tucson, AZ

Dr. Davis is a professor in the Department of Pharmacy Practice and Science at the University of Arizona College of Pharmacy. Her practice is with the Early Phase Clinical Trials Program at the University of Arizona Cancer Center, where she is also a member of the Cancer Prevention and Control Research Program. Dr. Davis received her BS in Pharmacy at the University of Arizona and her PharmD from the University of Kentucky. Her research focuses on drug development, drug resistance, and the influence of genomics and other factors that contribute to variability in drug disposition and patient outcomes in oncology. Dr. Davis is board certified in pharmacotherapy and oncology pharmacy.
Dr. Fausel is the Clinical Manager of the Oncology Pharmacy at the Indiana University, Simon Cancer Center in Indianapolis and oversees clinical and dispensing activities for oncology pharmacy services at Indiana University Health. He also serves as Chairman of the Board of the Hoosier Cancer Research Network, a non-profit organization that conducts clinical trials and translational research in cancer and is the administrative center of the Big Ten Cancer Research Consortium. Dr. Fausel is the Chair of a biomedical IRB and serves on the IRB Executive Committee for Indiana University.
Disclosures

Drs. Adams, Brenner, Davis, and Fausel have no relevant affiliations or financial relationships with a commercial interest to disclose.

The clinical reviewer, Megan May, PharmD, BCOP, has no actual or potential conflict of interest in relation to this program.

Susanne Batesko, RN, BSN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN-BC, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.
Learning Objectives

• **Appraise** current and emerging immuno-oncology agents and their roles in various cancer types

• **Describe** the biomarkers being examined to predict response to immunotherapy

• **Assess** emerging data concerning the safety and efficacy of different treatment combinations with immunotherapies in the treatment of oncologic disease states

• **Formulate** effective strategies to manage patient adherence and unique adverse events in both monotherapy and combination therapies
Case 1

JM is a 24-year-old male with Crohn’s disease that is well controlled on adalimumab.

- Presents with low-grade fevers and night sweats for 3 months, as well as a 15-kg weight loss.
- PET scan showed multiple positive nodes throughout the body. A nodal biopsy revealed advanced-stage (Stage IIIB) Hodgkin’s lymphoma with 9p24.1 and JAK2 amplification.
- JM received 6 cycles of AVD with brentuximab vedotin and had a complete response (CR).
- On the last cycle, he developed a cardiomyopathy with an ejection fraction of 35%, and, 3 months later, his lymphoma relapsed.
- JM was then treated with pembrolizumab with a CR after 3 months of therapy. His Crohn’s disease starts to flare at this time.
Pet scan at Relapse

PET scan image before treatment

Pet scan after 3 months of PD-1 inhibition

PET scan image after treatment
Will immunotherapy with pembrolizumab stimulate the lymphoma to grow?
Recognizing “Self” vs “Non-self”: “Normal” T-Cell Activation and Response

APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.

MHC/TCR + costimulation = ACTIVATION

Immune Checkpoint: CTLA4 Upregulates to Block Antigen Recognition


MHC/TCR + costimulation = ACTIVATION

Immune Checkpoint: PD-1/PD-L1 Upregulates to Inhibit T-cell Function

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Efficacy in Hodgkin’s Lymphoma

Nivolumab

Pembrolizumab

All patients had failed standard therapy and second-line treatment with transplant or brentuximab or both

ASCT, autologous stem-cell transplantation; ORR, objective/overall response rate.
FDA-Approved Checkpoint Inhibitor Immunotherapies

- CTLA4 antagonists
  - Ipilimumab

- PD-1 antagonists
  - Nivolumab
  - Pembrolizumab
  - Cemiplimab-rwlc

- PD-L1 antagonists
  - Atezolizumab
  - Avelumab
  - Durvalumab
Checkpoint Inhibitors Are Active Across Many Tumor Types

- Some of the cancer indications approved:
- Indications for use are increasing rapidly
- Role of combination therapy of CTLA4 and PD-1 inhibitors in some cases
- Development of combinations with cytotoxic chemotherapy are being developed with the first FDA approval for NSCLC

NSCLC, non-small cell lung cancer.
What other unique approaches are being used in hematology with checkpoint inhibitors?
Immune-Related Adverse Events (irAEs)

**Skin**
- Dermatitis exfoliative
- Erythema multiforme
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Vitiligo
- Alopecia

**Eye**
- Uveitis
- Iritis

**Pulmonary**
- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

**Endocrine**
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis

**Hepatic**
- Hepatitis, autoimmune

**Gastrointestinal**
- Colitis
- Enterocolitis
- Necrotizing colitis
- GI perforation

**Renal**
- Nephritis, autoimmune
- Renal failure

**Neurologic**
- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barre
- Myasthenia gravis–like syndrome

**Eye**
- Uveitis
- Iritis

GI, gastrointestinal.

What other mechanisms are involved in immuno-oncology?
CAR-t Methodology

T-cell collection from the patient

| Leukapheresis | Ship cells to manufacturer |

Clinical cell manufacturing facility

| Engineer T-cells with virus encoding CAR | Expand CAR-t cell population and harvest |

Deliver back to facility for infusion to the patient

| Handled by Stem Cell Lab | Infuse cells inpatient or outpatient with trained staff |

Chimeric Antigen Receptor (CAR) T-Cell

• The idea: *Put the entire T-cell stimulation process in 1 transmembrane receptor*
  1. Create antigen receptor
  2. Apply it to cytotoxic T-cells
  3. Link it DIRECTLY to T-cell intracellular cascades

• No need for co-stimulation or any other pathway

• FDA-approved agents:
  • Tisagenlecleucel (B-cell ALL)
  • Axicabtagene ciloleucel (B-cell NHL)

ALL, acute lymphocytic leukemia; NHL, non-Hodgkin’s lymphoma.

Case 1 Summary
Case 2

- KT is a 77-year-old male presenting with excruciating abdominal pain; he was hospitalized for a bowel obstruction and subsequently underwent a total colectomy and ileostomy. Pathology showed T4N2MX disease, a moderately differentiated adenocarcinoma. He had a history of Stage III colon cancer 12 years ago, which was treated with a partial colectomy followed by 6 months of adjuvant fluorouracil plus leucovorin.

- Two months ago, an MRI showed liver metastases. Tissue was sent for tumor molecular profiling and treatment was initiated with FOLFOX.

- He experienced disease progression after 6 cycles; his treatment was changed to nivolumab.
## Tumor Molecular Profile

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lineage- Relevant Biomarkers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSI</td>
<td>FA</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>NGS</td>
<td>High</td>
</tr>
<tr>
<td>Mismatch repair status*</td>
<td></td>
<td>Deficient</td>
</tr>
<tr>
<td>MLH1</td>
<td>IHC</td>
<td>Positive</td>
</tr>
<tr>
<td>MSH2</td>
<td>IHC</td>
<td>Negative</td>
</tr>
<tr>
<td>MSH6</td>
<td>IHC</td>
<td>Negative</td>
</tr>
<tr>
<td>PMS2</td>
<td>IHC</td>
<td>Positive</td>
</tr>
<tr>
<td>Total mutational load</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>KRAS</td>
<td>NGS</td>
<td>Mutation not detected</td>
</tr>
<tr>
<td>NRAS</td>
<td>NGS</td>
<td>Mutation not detected</td>
</tr>
<tr>
<td>BRAF</td>
<td>NGS</td>
<td>Mutation not detected</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lineage- Relevant Biomarkers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3CA</td>
<td>NGS</td>
<td>Mutated, pathogenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exon 21</td>
</tr>
<tr>
<td>ERBB2 (Her2/Neu)</td>
<td>NGS</td>
<td>Amplification not detected</td>
</tr>
<tr>
<td>PTEN</td>
<td>IHC</td>
<td>Positive</td>
</tr>
<tr>
<td>TS</td>
<td>IHC</td>
<td>Positive</td>
</tr>
<tr>
<td>TOPO1</td>
<td>IHC</td>
<td>Positive</td>
</tr>
<tr>
<td>ERCC1</td>
<td>IHC</td>
<td>Negative</td>
</tr>
</tbody>
</table>

| Other notable biomarker results |        |                         |
| PD-1             | IHC    | Negative | 0/HPF            |
| PD-L1            | IHC    | Negative | 0, 100%          |

Mismatch repair status is determined by the presence or absence of the repair proteins MLH1, MSH2, MSH6, and PMS2 by IHC. If any of these IHC’s is negative, mismatch repair status is considered deficient.

FA, fragment analysis; HPF, high power fields; IHC, immunohistochemistry; NGS, next-generation sequencing.
What biomarkers predict response to immunotherapy?
# Biomarker-Driven FDA-Approved Indications

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Biomarker</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>PD-L1 CPS ≥ 1</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>MSI-H or dMMR tumors</td>
<td>Nivolumab Pembrolizumab</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>PD-L1 CPS ≥ 1</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>NSCLC</td>
<td>High PD-1 expression (TPS) ≥ 50% (first-line)</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>PD-1 expression (TPS) ≥ 1%</td>
<td></td>
</tr>
<tr>
<td>Triple-negative breast cancer</td>
<td>PD-L1 expression ≥ 1%</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>PD-L1 expression ≥ 5%</td>
<td>Atezolizumab Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>PD-L1 CPS ≥ 10%</td>
<td></td>
</tr>
<tr>
<td>MSI-H cancer</td>
<td>MSI-H or dMMR tumors</td>
<td>Pembrolizumab</td>
</tr>
</tbody>
</table>

CPS, combined positive score; dMMR, deficient mismatch repair; MSI-H, microsatellite instability-high; TPS, tumor proportion score.
Biomarkers for PD-1 Blockade Sensitivity

Sensitivity to immune checkpoint blockade

Tumor immunogenicity
- Tumor neoantigens
- Tumor mutational load
- MSI-H/dMMR
- Viral antigens

Tumor microenvironment
- PD-L1
- Immune infiltrates
- Inflammatory genes/signature

Circulating markers
- Cytokines
- Inflammatory mediators
- Immune cells
- Myeloid-derived suppressor cells

Higher TMB Predicts Favorable Outcome with PD-1/PD-L1 Inhibitor

- Number of somatic mutations per megabase (Mb) of DNA
- Tumors with high TMB often have features of DNA damage, such as MSI-H or dMMR, but not always

TMB, tumor mutational burden.

Case 2: The tumor is MSI-H and dMMR. How effective is immunotherapy?
Nivolumab for MSI-H/dMMR mCRC

- Checkmate 142 (second-line for mCRC w/ MSI-H or dMMR)
- Open label phase II trial: failed 1+ therapies w/ 5FU and Oxaliplatin or irinotecan (54% of patients had 3+ prior therapies)

Second-line ramucirumab/FOLFIRI: PFS = 5.7 mo; OS = 13.3 mo.

Pembrolizumab Activity Against Multiple MSI-H/dMMR Solid Tumors

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>N</th>
<th>n (%)</th>
<th>95% CI</th>
<th>DOR range (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>90</td>
<td>32 (36%)</td>
<td>(26%, 46%)</td>
<td>(1.6+, 22.7+)</td>
</tr>
<tr>
<td>Non-CRC</td>
<td>59</td>
<td>27 (46%)</td>
<td>(33%, 59%)</td>
<td>(1.9+, 22.1+)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>14</td>
<td>5 (36%)</td>
<td>(13%, 65%)</td>
<td>(4.2+, 17.3+)</td>
</tr>
<tr>
<td>Biliary cancer</td>
<td>11</td>
<td>3 (27%)</td>
<td>(6%, 61%)</td>
<td>(11.6+, 19.6+)</td>
</tr>
<tr>
<td>Gastric or GE junction cancer</td>
<td>9</td>
<td>5 (56%)</td>
<td>(21%, 86%)</td>
<td>(5.8+, 22.1+)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>6</td>
<td>5 (83%)</td>
<td>(36%, 100%)</td>
<td>(2.6+, 9.2+)</td>
</tr>
<tr>
<td>Small intestinal cancer</td>
<td>8</td>
<td>3 (38%)</td>
<td>(9%, 76%)</td>
<td>(1.9+, 9.1+)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>PR, PR</td>
<td></td>
<td>9.8+</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>PR, SD</td>
<td></td>
<td>18.2+</td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>1</td>
<td>NE</td>
<td></td>
<td>7.5+</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>1</td>
<td>PR</td>
<td></td>
<td>8.9+</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>1</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal adenocarcinoma</td>
<td>1</td>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small cell lung cancer (SCLC)</td>
<td>1</td>
<td>CR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ORR = 40%, CR = 7%**

Summary from 5 trials – All patients had 1+ prior regimens

Why are MSI-H and dMMR tumors sensitive to immunotherapy?
dMMR Leads to MSI-H Tumors

- Inactivation of DNA mismatch repair genes leads to absent or dysfunctional MMR protein → dMMR
- Unrepaired DNA replication errors accumulate, causing abnormal lengths of microsatellite repeats in DNA sequences across the genome → microsatellite instability
- MSI-H tumors harbor mutations in at least 2 of 5 specific microsatellites
- dMMR tumors are hypermutated with accumulated nucleotide base mismatches, indels, and frameshift mutations that can generate immunogenic neoantigens

How does the tumor microenvironment influence response to immunotherapy?
The Tumor Microenvironment is Complex

Tumor Immune Infiltrate is Critical for Immune Checkpoint Inhibitor (ICI) Activity

• Tumor neoantigens associated with increased T-cell activation and immune cell infiltration in an “inflamed” tumor microenvironment
  • Compartmentalization of immune cells in tumor center and at the invasive margins
  • Dense T-lymphocyte infiltrate – CD3+, CD8+, CD45RO+, Th1
  • Interferon-γ
• Involvement of other cell subsets (e.g., Treg cells, macrophages) may confer better or worse prognosis, depending on the context


Th1, T helper cells; Treg, regulatory T-cells.
Is PD-L1 expression required for tumor response to immune checkpoint inhibition?
High Levels of PD-L1 Expression are Associated with Better Outcomes with PD-1/PD-L1 Inhibition

• Reflects adaptive resistance to T-cell infiltration into tumors
• Identifies tumors most likely to respond to immune checkpoint inhibition
• Up to 20% of patients with tumors that stain negative or low for PD-L1 expression respond to ICIs
• Multiple factors influence PD-L1 expression
  • Antibody
  • Test platform
  • Positivity threshold
  • Cells of interest
  • Tumor material

What are emerging biomarker strategies?
Immunoscore Defines Immune Infiltrate in Tumors

- Classification based on standardized quantification of CD3+ and CD8+ T-cell densities at tumor specimen center (CT) and invasive margins (IM)
- Prognostic biomarker to estimate risk of recurrence in patients with Stage I-III colon cancer
- Potential predictive biomarker

Emerging Biomarkers

**Gene expression profiles**

- Signatures profiling inflammation-specific genes
  - Gamma interferon-inducible genes – define “hot,” inflamed tumors
- Immune gene signatures – T-cell, B-cell, natural killer (NK) cell involvement; T-cell surface markers
- Cytokines and chemokines

**Peripheral blood**

- Myeloid-derived suppressor cells
  - Recruited to tumor microenvironment
  - Suppress effector cell responses
  - Present in tumor tissue and blood
- Circulating tumor DNA

Next-Generation Sequencing

- PD-L1 protein expression is dynamic and an imperfect predictor of tumor response to PD-L1 blockade
- Next-generation whole-exome and targeted gene panel sequencing can identify TMB and specific genetic mutations
Case 2 Summary
Combination Treatments
ICI + Chemotherapy
ICI + Radiation Therapy (RT)
ICI + ICI
ICI + Targeted Therapy
The New Chapter in Cancer Treatment

Diseases Utilizing ICI Treatment Combinations

- **NSCLC**
  - ICI + chemo
  - ICI + RT
  - ICI + ICI

- **Melanoma**
  - ICI + ICI
  - ICI + RT
  - ICI + targeted

- **SCLC**
  - ICI + chemo

- **Renal**
  - ICI + ICI
  - ICI + targeted

- **Colorectal**
  - (MSI-H or dMMR)
  - ICI + ICI

- **Head & neck**
  - ICI + targeted
  - ICI + RT

- **Other cancer types**
  - ICI + targeted
  - ICI + RT
Case 3

- AF is a 71-year-old female with newly diagnosed metastatic non-squamous NSCLC. She presents with a progressive weakness, fatigue, headaches, and lightheadedness over the past 2 months. She also reports a 19-lb weight loss over the past year. Chest x-ray in ED revealed a suspicious mass.
- Chest CT revealed a 3.5-cm spiculated left hilar mass, 3 left upper lobe nodules (largest 16 mm), 3-mm right lower lobe mass, and axillary LAD.
- Brain MRI revealed 3 CNS metastases (largest 6 mm) in left superior frontal gyrus.
- Bone scan showed an indeterminate left humeral lesion.
- CT-guided left hilar mass biopsy revealed adenocarcinoma.
- Her PMH is significant for COPD, TIA.
- AF denies alcohol use, but she is a 50+ pack-year smoker (1 pk/day but recently decreased to 0.5 pk/day)
- Her sister has NHL, and her father has lung cancer.
Case 3

- AF meets with her outpatient oncologist 2 weeks later. Her CT scans, MRI, and pathology are reviewed. AF understands that she has a treatable (not curable) lung cancer. Her oncologist states she would like to wait for the PD-L1 testing and molecular studies to determine the optimal treatment plan.

- AF meets with a radiation oncologist for her CNS metastases the next day. Given that she has only 3 lesions and is symptomatic, a single fraction of stereotactic radiosurgery (SRS) will be scheduled for next week.

- One week after SRS, AF meets with her oncologist:
  - PET/CT scan reveals disease in her distant lymph nodes, bilateral adrenal involvement, and pelvic bone.
  - PD-L1 testing is indeterminant (poor tissue sample).
  - NGS Guardant360 reveals an uncommon K-RAS (K117N) variant and TP53 mutations.

- Based on AF’s workup, her oncologist recommends first-line treatment with carboplatin (AUC=5), pemetrexed 500 mg/m², and pembrolizumab 200 mg every 3 weeks for 4 cycles (based on the Keynote 189 trial) and discusses the potential benefit and toxicities with her. AF agrees to treatment with this combination immunotherapy and chemotherapy regimen. She will receive vitamin B12 and a folic acid prescription today and return to clinic next week to begin treatment.
# First-Line NSCLC ICI + Chemo Combinations

<table>
<thead>
<tr>
<th>FDA Indication</th>
<th>Trial and Treatments</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Non-squamous cell NSCLC (first-line) | Keynote-189 (Phase 3; n=616)  
Cisplatin (or carboplatin) + pemetrexed with pembrolizumab (n=410) vs.  
cisplatin (or carboplatin) + pemetrexed without pembrolizumab (n=206) | 12-month OS  
PD-L1 <1%: 62% vs. 52%  
(HR=0.59, 95% CI 0.38-0.92)  
PD-L1 1-49%: 72% vs. 51%  
(HR=0.55, 95% CI 0.34-0.9)  
PD-L1 >50%: 73% vs. 48%  
(HR=0.42, 95% CI 0.26-0.68) |
| Non-squamous cell NSCLC (first-line) | IMpower150 (Phase 3; n=1202)  
Carboplatin, paclitaxel, bevacizumab with atezolizumab (n=359) vs.  
carboplatin, paclitaxel, bevacizumab without atezolizumab (n=337) | OS  
19.2 mos vs. 14.7 mos  
(HR=0.78, 95% CI 0.64-0.96)  
PFS  
8.3 mos vs. 6.8 mos  
(HR=0.62, 95% CI 0.52-0.74) |
| Squamous cell NSCLC (first-line) | Keynote-407 (Phase 3; n=559)  
Carboplatin plus paclitaxel (or nab-paclitaxel) with pembrolizumab (n=278) vs.  
carboplatin plus paclitaxel (or nab-paclitaxel) without pembrolizumab (n=281) | OS  
15.9 mos vs. 11.3 mos  
(HR=0.64, 95% CI 0.49-0.85)  
PFS  
6.4 mos vs. 4.8 mos  
(HR=0.56, 95% CI 0.45-0.7) |

HR, hazard ratio; OS, overall survival.


Does this therapy (Keynote 189) favor OS?

**AF:**
- 71 years old
- Female
- ECOG PS = 1
- Current smoker
- Brain mets (at diagnosis)
- PD-L1 = unknown
- Carboplatin

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/ No. of Patients</th>
<th>Hazard Ratio for Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>235/616</td>
<td>0.49 (0.38–0.64)</td>
</tr>
<tr>
<td>Age (&lt;65 yr)</td>
<td>133/312</td>
<td>0.43 (0.31–0.61)</td>
</tr>
<tr>
<td>Age (≥65 yr)</td>
<td>102/304</td>
<td>0.64 (0.43–0.95)</td>
</tr>
<tr>
<td>Sex (Male)</td>
<td>143/363</td>
<td>0.70 (0.50–0.99)</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>92/253</td>
<td>0.29 (0.19–0.44)</td>
</tr>
<tr>
<td>ECOG performance-status score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>74/266</td>
<td>0.44 (0.28–0.71)</td>
</tr>
<tr>
<td>1</td>
<td>159/346</td>
<td>0.53 (0.39–0.73)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current or former</td>
<td>211/543</td>
<td>0.54 (0.41–0.71)</td>
</tr>
<tr>
<td>Never</td>
<td>24/73</td>
<td>0.23 (0.10–0.54)</td>
</tr>
<tr>
<td>Brain metastases at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51/108</td>
<td>0.36 (0.20–0.62)</td>
</tr>
<tr>
<td>No</td>
<td>184/508</td>
<td>0.53 (0.39–0.71)</td>
</tr>
<tr>
<td>PD-L1 tumor proportion score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>84/190</td>
<td>0.59 (0.38–0.92)</td>
</tr>
<tr>
<td>≥1%</td>
<td>135/388</td>
<td>0.47 (0.34–0.66)</td>
</tr>
<tr>
<td>1–49%</td>
<td>65/186</td>
<td>0.55 (0.34–0.90)</td>
</tr>
<tr>
<td>≥50%</td>
<td>70/202</td>
<td>0.42 (0.26–0.68)</td>
</tr>
<tr>
<td>Platinum-based drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>176/445</td>
<td>0.52 (0.39–0.71)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>59/171</td>
<td>0.41 (0.24–0.69)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Group Performance Status.

Is the timing of chemotherapy and immunotherapy optimized?
Keynote 189: Dosing Schema

Non-squamous cell NSCLC (known PD-L1 status; no EGFR or ALK mutations) – ECOG PS 0-1; treatment naïve

**Randomized 2:1**
(n=616)

Primary end points: OS, PFS
Secondary end points: response rate; DOR; safety

- **Placebo +** pemetrexed 500 mg/m² + carboplatin AUC 5 (or cisplatin 75 mg/m²) Q3W x 4 cycles (n=206)

- **Pembrolizumab 200 mg +** pemetrexed 500 mg/m² + carboplatin AUC 5 (or cisplatin 75 mg/m²) Q3W x 4 cycles (n=410)

- **Pembrolizumab 200 mg Q3W** for up to 31 cycles + pemetrexed 500 mg/m² Q3W

- **Placebo (normal saline) Q3W** for up to 31 cycles + pemetrexed 500 mg/m² Q3W

- **Pembrolizumab 200 mg Q3W** for up to 35 cycles

Keynote 189: Overall Survival

Note: the survival curves begin to separate during combination therapy.

Extensive stage SCLC – ECOG PS 0-1; chemotherapy naïve

Randomized 1:1 (n=403)

Atezolizumab 1200 mg d1 + carboplatin AUC 5 d1 + etoposide 75 mg/m² d1-3 Q3W x 4 cycles (n=202)

Placebo Q3W d1 (until disease progression)

Atezolizumab 1200 mg Q3W d1 (until disease progression)

Placebo Q3W d1 (until disease progression)

Primary end points: OS, PFS
Secondary end points: overall response; DOR

IMpower133: Overall Survival

Note: The survival curves do not separate until during maintenance treatment

Synergy with Radiation
Chemoradiotherapy Outcomes

NPC 95-01 (Phase III) – Concurrent (n=100) versus sequential (n=101) treatment with RT and platinum doublet chemotherapy in unresectable Stage III NSCLC

Concurrent chemoradiotherapy
Median OS = 16.3 months
12 month DFS = 42%
ORR = 49%
CR, PR, SD = 84%

Locally advanced, unresectable (Stage III) NSCLC with CR, PR, and SD after definitive chemoradiotherapy with platinum doublet and concurrent radiation (54 to 66 Gy)

Stage III NSCLC with CR, PR, and SD after definitive chemoradiotherapy
Randomized 2:1
Stratified by age, sex, and smoking history
(n=709)

Durvalumab 10 mg/kg IV Q2W d1 (up to 12 months) (n=473)

Placebo IV Q2W d1 (up to 12 months) (n=236)

Primary end points: OS, PFS
Secondary end points: multiple

PACIFIC: Overall Survival


Median follow up = 25.5 months
Synergy with 2 Checkpoint Inhibitors
CheckMate 227 (Part 1): Dosing Schema

First-line nivolumab + ipilimumab in Stage IV or recurrent NSCLC (no EGFR or ALK mutations/ECOG PS = 0-1)

Randomized 1:1:1 (n=1189)

- Nivolumab 3 mg/kg IV Q2W + ipilimumab 1 mg/kg IV Q6W
- Chemotherapy (platinum doublet) Q3W x 4 cycles
- Nivolumab 240 mg IV Q2W

Primary end points: PFS; OS

Stratified by histology: squamous vs non-squamous

Randomized 1:1:1 (n=550)

- Nivolumab 3 mg/kg IV Q2W + ipilimumab 1 mg/kg IV Q6W
- Chemotherapy (platinum doublet) Q3W x 4 cycles
- Nivolumab 240 mg IV Q2W + chemotherapy (platinum doublet) Q3W x 4 cycles

TMB

PD-L1

≥1%

PD-L1

<1%

First-Line Nivolumab/Ipilimumab with High TMB (≥10 mutations/Mb)

**ORR**
- Nivo/Ipi = 45%
- Chemo = 27%

**DOR @ 12 mo**
- Nivo/Ipi = 68%
- Chemo = 25%

Synergy with Targeted Therapy
JAVELIN Renal 101

Phase III, randomized, open-label in advanced renal-cell carcinoma (clear cell component)

Previously untreated advanced renal-cell carcinoma with clear cell component
ECOG PS 0-1
Geographic region (n=886)

Randomized 1:1

Avelumab 10 mg/kg IV Q2W (x 3 doses = 6 week cycles) + axitinib 5 mg PO BID (continuous dosing)
(n=442; n=270 PD-L1+)

Sunitinib 50 mg PO daily (continuous for 4 weeks then 2 weeks off = 6-week cycle)
(n=444; n=290 PD-L1+)

Primary end points: PFS, OS (in PD-L1+ status)
Secondary end point: PFS, OS (not based on PD-L1 status)

PD-L1 + tumors 560/886 = 63.2%

A Patients with PD-L1–Positive Tumors

<table>
<thead>
<tr>
<th>Months</th>
<th>Progression-free Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>24</td>
<td>1</td>
</tr>
</tbody>
</table>

Median Progression-free Survival (95% CI)

- Avelumab+Axitinib: 13.8 (11.1–NE) months
- Sunitinib: 7.2 (5.7–9.7) months

Stratified hazard ratio for disease progression or death: 0.61 (95% CI, 0.47–0.79), P<0.001

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Avelumab+Axitinib</th>
<th>Sunitinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>270</td>
<td>227</td>
<td>290</td>
</tr>
<tr>
<td>205</td>
<td>154</td>
<td>210</td>
</tr>
<tr>
<td>120</td>
<td>76</td>
<td>174</td>
</tr>
<tr>
<td>53</td>
<td>32</td>
<td>119</td>
</tr>
<tr>
<td>32</td>
<td>23</td>
<td>85</td>
</tr>
<tr>
<td>13</td>
<td>13</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Two New ICI + Targeted Trials in Advanced Renal Cell Carcinoma: PFS

**JAVELIN Renal 101:**
Avelumab + axitinib vs. sunitinib

**Keynote-426:**
Pembrolizumab + axitinib vs. sunitinib

**Median PFS:**
Avelumab + axitinib = 13.8 mos  
Sunitinib = 8.4 mos  
HR = 0.69; 95% CI, 0.56 to 0.84; P<0.001

**Median PFS:**
Pembrolizumab + axitinib = 15.1 mos  
Sunitinib = 11.1 mos  
HR = 0.69; 95% CI, 0.57 to 0.84; P<0.001

What combination is most promising?
Case 3 Summary
Immunotherapy
Adverse Events
Case 4

- RS is a 59-year-old male with metastatic melanoma who presents with shortness of breath and a cough.
- RS was diagnosed with metastatic melanoma 10 weeks ago. Initial presentation with right hip pain that was suspicious for a metastatic lesion upon work-up. A CT scan identified bilateral pulmonary nodules and chest wall nodules, as well as an abdominal mass. Pathology from the bone mass biopsied showed melanoma. Follow-up genetic testing demonstrated the tumor to be BRAF V600E negative.
- Ipilimumab + nivolumab was started 8 weeks prior to this visit: he has completed 4 cycles without a problem.
- His past medical history is significant for COPD, HTN, CAD, and HLD.
- RS stopped smoking 6 months ago when diagnosed w/ COPD (68 pack-year history [~2 pk/day since 15 years old]).
Case 4

- Medications: losartan 50 mg po daily, metoprolol 50 mg po bid, aspirin 325 mg po daily, simvastatin 40 mg po qhs, tiotropium 2 puffs daily, albuterol 1-2 puffs q4h prn; NKDA

- Labs:

<table>
<thead>
<tr>
<th>LABS (last 24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>127</td>
</tr>
<tr>
<td>4.0</td>
</tr>
</tbody>
</table>

- Radiology: CT/PET – diffuse opacities (ground glass appearance) and small growth of pre-existing pulmonary lesions; abdominal mass unchanged; bone lesions visualized
## Adverse Events Guideline

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Asymptomatic, confined to 1 lobe of the lung or 25% of lung parenchyma; clinical or diagnostic observations only</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>Symptomatic, involves more than 1 lobe of the lung or 25%-50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td>Severe symptoms, hospitalization required; involves all lung lobes or &gt;50% of lung parenchyma; limiting self-care ADL; oxygen indicated</td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Life-threatening respiratory compromise, urgent intervention indicated (intubation)</td>
<td></td>
</tr>
</tbody>
</table>

Case 4: Considerations

1. Is this a COPD exacerbation?
2. Is this an infectious process?
3. Is this drug-induced pneumonitis?
4. Is this a pulmonary embolism?
Pneumonitis from Nivo/Ipi

*Pneumonitis*: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging); no radiographic features are pathognomonic for pneumonitis

**Diagnostic work-up** should include the following: CXR, CT, pulse oximetry
For G2 or higher, may include the following *infectious work-up*: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Nivo/Ipi group</th>
<th>Nivolumab group</th>
<th>Ipilimumab group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>7%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>


CT, computed tomography; CXR, chest X-ray.
G2 Nivo/Ipi Pneumonitis Treatment

- ASCO/NCCN guideline
- Hold ICI until resolution to G1 or less
- Prednisone 1-2 mg/kg/d and taper by 5-10 mg/week over 4-6 weeks
- Consider bronchoscopy with bronchoalveolar lavage (BAL)
- Consider empirical antibiotics
- Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR
- If no clinical improvement after 48-72 hours of prednisone, treat as G3
G3 Nivo/lpi Pneumonitis Treatment

- ASCO/NCCN guideline
- **Permanently discontinue** ICI
- Empirical antibiotics
- (Methyl)prednisolone IV 1-2 mg/kg/d
  - If no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide
  - Taper corticosteroids over 4-6 weeks
- Pulmonary and infectious disease consults if necessary
- Bronchoscopy with BAL +/- transbronchial biopsy
- Patients should be hospitalized for further management

What if RS Does Not Respond to Steroids?

Would you add:

1. Infliximab?
2. Mycophenylate mofetil?
3. IVIG?
4. Cyclophosphamide?
5. Other?

IVIG, intravenous immunoglobulin.
RS: Re-Challenge after Response

- Do you have a favorite steroid taper schedule?
  - Any pearls to help patients maintain compliance?
- Would you restart:
  - Nivolumab?
  - Ipilimumab?
  - Both?
- How do you time re-initiation of an ICI during a steroid taper?
• ICIs are broadly used
• Indiscriminant re-invigoration of exhausted T-cells can lead to irAEs
• Current research is aimed at optimizing outcomes
  • Biomarker selection of patients
  • Combination approaches
• Proper counseling and monitoring for irAEs is critical to optimize benefit (catch and intervene while G2)
• Adverse events that occur with combination therapy can be challenging
• Progressive disease with combination therapy can be challenging
Thank you!