ECONOMIC AND CLINICAL OUTCOMES ASSESSMENT OF IMMUNO-Oncology Agents

A Guide for Payer Decision Makers

Jointly provided by

This activity is supported by independent educational grants from Bristol Myers Squibb and Merck & Co., Inc.

Live Webcast
Monday, June 15, 2020
12:30 PM – 2:00 PM ET
Welcome

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC
<table>
<thead>
<tr>
<th>Agenda</th>
</tr>
</thead>
</table>
| **Opening Comments/Overview**  
*Edmund Pezalla, MD, MPH* |

| Clinical Update on the Evolving Immuno-Oncology Treatment Paradigm  
*Yung Lyou, MD, PhD* |

| Evidence-based Decision Making in a Cost Conscience Environment  
*Edmund Pezalla, MD, MPH* |

| Medical and Pharmacy Management Strategies to Enhance Outcomes Requiring Treatment with Immuno-Oncology Agents  
*Edmund Pezalla, MD, MPH* |

| Faculty Idea Exchange & Question and Answer Session  
*All Faculty* |

| Key Takeaways and Closing Comments  
*Adjournment* |
Learning Objectives

• Characterize the role of the immune system in immunosurveillance and elimination of malignant cell lines
• Explain the mechanisms of action of novel immuno-oncology agents such as PD-1 and PD-L1 inhibitors and CAR-T therapies
• Describe key outcomes measures in immuno-oncology and the importance of cumulative assessment of outcomes
• Apply comprehensive analyses of emerging clinical trial data for checkpoint inhibitors and CAR-T therapies
• Illustrate current and proposed payer initiatives for the funding and management of checkpoint inhibitors and CAR-T therapies
Clinical Update on the Evolving Immuno-Oncology Treatment Paradigm

Yung Lyou, MD, PhD
Medical Oncologist
Assistant Clinical Professor
Department of Medical Oncology
City of Hope
The Evolution of Cancer Treatment

- Single Agent Chemotherapy
- Combination Chemotherapy
- Combination Chemo-radiation
- Oral Chemotherapy
- Molecularly Targeted Treatments
- Immune Checkpoint Inhibitors
What role(s) do T cells play in the immune response to cancer?

1) Elimination of malignancy
2) Tumor antigen presentation
3) Immunosurveillance
4) Antibody production
5) 1 and 3
6) All of the above
Immunosurveillance and Elimination of Malignancy: The Central Role of T-cells

The Role of T cells in Cancer and Metastasis

The Immune Response to Tumors

- Tumor cells
- Dying tumor cells – releasing antigen
- MHC-antigen / TCR (1st signal)
- B7 (CD80/86)/ CD28 (2nd signal)
- Proliferation ▲
- Cytokines ▲
- Accelerating immune response ▲

MHC, major histocompatibility complex; TCR, t-cell receptor.

The Immune Response to Tumors and the Role of Immune Checkpoint Inhibitors (ICIs)

Antigen-presenting cell taking up cancer antigen and \textit{activating T-cell response}

MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, t-cell receptor.

Enhancing the T cell response: CTLA-4 and PD-1 Pathway Blockade


- Anti-PD1: Nivolumab, Pembrolizumab
- Anti-PDL1: Atezolizumab, Avelumab, Durvalumab
- Anti-CTLA-4: ipilimumab
Immune Checkpoint Inhibitors (ICI)

- Immunomodulatory agents that target key "immune checkpoints"
  - Regulate the stimulation or inhibition of an immune response
  - Exploited by tumors to evade cytotoxic T cells

- ICI proteins and associated ligands
  - CTLA-4
  - PD-1
  - PD-L1

ICIIs “take the brakes off” the immune system and allow it to go into overdrive and attack cancer cells

MoA of PD-1/ PD-L1 inhibitors ICI

- Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check.
- The binding of PD-L1 to PD-1 prevents T cells from killing tumor cells.
- Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells.

MoA of CTLA-4 inhibitors ICI

- Checkpoint proteins, such as B7-1/B7-2 on antigen presenting cells and CTLA-4 on T cells, help keep immune responses in check.

- The binding of B7-1/B7-2 to CTLA-4 keeps the T cells in the inactive state so they are not able to kill tumor cells.

- Blocking the binding of B7-1/B7-2 to CTLA-4 with an immune checkpoint inhibitor (anti-CTLA-4 antibody) allows the T cells to be active and to kill tumor cells (right panel).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Anti–CTLA-4</td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Anti–PD-1</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Anti–PD-L1</td>
</tr>
<tr>
<td>Avelumab</td>
<td></td>
</tr>
<tr>
<td>Durvalumab</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Indications</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>NSCLC, SCLC, breast CA (TNBC)</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Merkel cell carcinoma, urothelial carcinoma, advanced RCC</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>NSCLC, urothelial carcinoma</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Metastatic NSCLC, Metastatic Melanoma, Advanced RCC, Small Cell Lung CA, Recurrent or Metastatic SCC of the Head and Neck, HCC, Locally Advanced or Metastatic Urothelial Carcinoma, MSI-H/dMMR Metastatic colorectal CA, Relapsed or Progressed cHL</td>
</tr>
<tr>
<td>Cemiplimab-rlwc</td>
<td>advanced cutaneous SCC</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>Melanoma, RCC, MSI-H/dMMR colorectal CA, HCC</td>
</tr>
</tbody>
</table>
Pembrolizumab plus Axitinib versus Sunitinib for Advanced Metastatic Renal-Cell Carcinoma

Durvalumab in Stage III NSCLC: A: PFS and B: Survival: ITT population

A. PFS in the ITT Population

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>16.8 (13.0-18.1)</td>
<td>5.6 (4.6-7.8)</td>
</tr>
<tr>
<td>12-mo PFS, % (95% CI)</td>
<td>55.9 (51.0-60.4)</td>
<td>35.3 (29.0-41.7)</td>
</tr>
<tr>
<td>18-mo PFS, % (95% CI)</td>
<td>44.2 (37.7-50.5)</td>
<td>27.0 (19.9-34.5)</td>
</tr>
</tbody>
</table>

B. OS in the ITT Population

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n/N</td>
<td>183-478</td>
<td>116-237</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>NR (34.7 NR)</td>
<td>28.7 (22.9 NR)</td>
</tr>
<tr>
<td>12-mo OS Rate (95% CI), %</td>
<td>83.1 (79.4-86.2)</td>
<td>75.3 (69.2-80.4)</td>
</tr>
<tr>
<td>24-mo OS Rate (95% CI), %</td>
<td>66.3 (61.7-70.4)</td>
<td>55.6 (48.9-61.8)</td>
</tr>
<tr>
<td>Stratified HR for death (99.73% CI)</td>
<td>0.68 (0.47-0.997)</td>
<td></td>
</tr>
</tbody>
</table>

Stratified HR = 0.52 (95% CI, 0.42-0.65)
Two-sided P < .001

Small Cell Lung Cancer Overall Survival: Chemotherapy + Atezolizumab vs Chemotherapy + Placebo:

Atezolizumab: Metastatic TNBC: Progression-Free Survival

Multiple mechanisms that limit autoimmunity need to be overcome in cancer immunotherapy.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab + Pembrolizumab</td>
<td>Still in clinical trials</td>
</tr>
<tr>
<td>Ipilimumab + Nivolumab</td>
<td>approved for unresectable or metastatic melanoma, hepatocellular carcinoma (HCC), advanced renal cell carcinoma (RCC) and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) as well as non-small cell lung cancer (NSCLC)</td>
</tr>
<tr>
<td>Ipilimumab + Cemiplimab</td>
<td>Still in clinical trials</td>
</tr>
</tbody>
</table>

2. Opdivo [prescribing information]; Princeton, NJ: Bristol-Myers Squibb;2020.;
3. Yervoy [prescribing information]; Princeton, NJ: Bristol-Myers Squibb;2020;
4. Libtayo [prescribing information]; Tarrytown, NY: Regeneron Pharmaceuticals and Sanofi-Aventis;2018.;
Overall Survival and Progression Free Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma (CHECKMATE 067)

Nivolumab Plus Ipilimumab as First-Line Treatment for mRCC: Overall Survival

Chimeric antigen receptors (CARs) are fusion molecules typically composed of the following:

- An extracellular single chain variable fragment (scFv) of a monoclonal antibody (mAb) specific for a surface molecule on the tumor cell
- A spacer domain that provides flexibility and optimizes T cell and target cell engagement
- A transmembrane domain
- Signaling modules that trigger T cell effector functions
Chimeric Antigen Receptor T-cell (CAR-T) Therapy Overview and MoA

- CAR-T cells are genetically engineered from a patient’s own T cells.

- These genetically engineered T cells can identify the target tumor associated antigens and trigger an immune response.

- Currently available CAR-T therapies target B cell cancers.
## FDA Approved CAR-T Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Binding Target</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tisagenlecleucel</td>
<td>CD19</td>
<td>Acute lymphoblastic leukemia, non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>Axicabtagene ciloleucel</td>
<td>CD19</td>
<td>Large B-cell lymphoma, Diffuse large B-cell lymphoma (DLBCL)</td>
</tr>
</tbody>
</table>

Tisagenlecleucel [prescribing information]; 2018.; Axicabtagene ciloleucel [prescribing information]; 2019.
Axicabtagene Ciloleucel in Refractory Aggressive Non-Hodgkin Lymphoma

Complete Response (CR) and Objective Response Rate (ORR) Compared with Traditional Salvage Therapies

The immune system is capable of recognizing and eliminating tumor cells in the tumor microenvironment.

Immune balance is maintained through the combination of activating and inhibitory signaling pathways that modulate the activity of effector cells (cytotoxic T cells and NK cells).

Immuno-oncology agents that utilize the cytotoxic T cell response include checkpoint inhibitor antibodies aimed at CTLA-4 and PD-1/L1 and CAR-T therapies.

These agents have demonstrated promise in the treatment of several tumor types, with findings often characterized by extended OS in the long-term.

Combination regimens offer further potential for future regimens.
Evidenced-based Decision Making in a Cost Conscious Environment

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC
Which of the following best describes your area of greatest educational need with regards to immuno-oncology?

1. Defining the key clinical outcomes measures for IO regimens.
2. Assessing the overall value of individual agents or regimens that can lend insight to payer-led management interventions.
4. Guideline recommendations and general management for immune-related adverse events.
Key Outcomes Measures in Immuno-Oncology and the Importance of Cumulative Assessment of Outcomes

- Delayed onset of responses
- Different immune-related adverse events (irAEs)
- Often require genetic testing to ensure that therapies will be successful
Better selection of patients

Combine treatments to increase immune recognition

Combine treatments to decrease immune ESCAPE
Moving the Plateau Up

Need for Biomarkers

Responses to immunotherapy are durable

Some patients that initially respond to immunotherapy eventually relapse

Biomarkers to determine which patients are most likely to respond to immune checkpoint inhibitors (ICIs) can improve patient selection and ensure that patients receive the most effective therapy.
Predicting Response to Immunotherapies

• Tumor Neoantigens ("inflamed" tumor microenvironment)
• Biomarkers
  • Emerging biomarkers
  • Allow better selection of patients
• Tumor Mutational Burden (TMB)
• Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) status
• Tumor Microenvironment
• Next-generation sequencing (for TMB)
• Combination of techniques for predicting success is currently needed

Higher Tumor Mutational Burden (TMB) Predicts Favorable Outcomes With PD-1/PD-L1 Inhibitor

- TMB is the number of somatic mutations per Mb of DNA
- Tumors with high TMB often have features of DNA damage, such as MSI-H or dMMR, but not always

Mb, megabase; TMB, tumor mutational burden.
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

Emerging Biomarkers: Peripheral Blood

Myeloid-derived suppressor cells (MDSCs)
- Recruited to tumor microenvironment
- Suppress effector cell responses
- Present in tumor tissue and blood

Circulating tumor DNA (ctDNA)

• Next-generation whole exome and targeted gene panel sequencing can identify TMB and specific genetic mutations

High Levels of PD-L1 Expression are Associated with Better Outcomes with PD-1/PD-L1 Inhibition

- Due to the 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

Biomarker testing for the PD-L1 target is key before treating tumors with PD-1/ PD-L1 inhibitors

It is recommended by the NCCN guidelines for multiple cancers
The Role of Companion and Complementary Diagnostics

**Companion Diagnostics**

- Specified on the drug label (21 therapies to date, >50% in NSCLC)
  - e.g., ALK+ for crizotinib in NSCLC
- Typically among inclusion criteria for pivotal trials
- Required for PA

**Complementary Diagnostics**

- Predictive of response but not required
  - KRAS/NRAS/BRAF for cetuximab in colorectal cancer
- Assay may be integrated into pivotal trials but not part of inclusion criteria
- May be incorporated into more rigorous PA requirements

A number of PD-1/L1 checkpoint inhibitors feature companion and complementary diagnostics that may be incorporated into PA criteria

These assays are based on PD-L1 titers predictive of response

Role of lab-developed tests vs. FDA approve tests
Companion and Complementary Diagnostics for IO

**Companion Diagnostics:**

- PD-L1 immunohistochemical (IHC) 22C3 pharmDx assay for pembrolizumab
- Ventana PD-L1 for atezolizumab

**Complementary Diagnostics:**

- PD-L1 IHC 28-8 pharmDx for nivolumab
- Ventana PD-L1 for durvalumab

Note: higher levels of PD-L1 are associated with better outcomes with PD-1/PDL1 inhibition

ICI: Immune-Related Adverse Events (irAEs)

- May be due to cytokine release by activated T cells
- May be unfamiliar to clinicians
- Requires a multidisciplinary approach
- Can be serious
- Requires prompt recognition and treatment
- Requires patient and HCP education

Activation of the immune system against tumors can result in a novel spectrum of irAEs

Guideline Recommendations for irAEs


POSITION ARTICLE AND GUIDELINES

Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group


# General Management of Adverse Events

<table>
<thead>
<tr>
<th>irAE</th>
<th>ICI therapy</th>
<th>Immunosuppressants</th>
<th>Other treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Discontinue if hypophysitis, pneumonitis, and/or sarcoidosis; Consider holding if renal; Hold if neurologic, aplastic anemia, acquired hemophilia; Continue for all others</td>
<td>Prednisone 0.5-1 mg/kg/day if acquired hemophilia</td>
<td>Topical steroids(^a), oral antihistamines(^b), topical emollients if dermatologic; Loperamide if gastrointestinal(^c); Thyroid hormone supplementation(^d) if hypothyroidism; Beta-blockers for symptomatic hyperthyroidism(^e); insulin therapy if hyperglycemia; Oral fluids, loperamide, hormone replacement therapy(^f) if hypophysitis; Consider artificial tears if ocular; Analgesics(^g) if rheumatologic</td>
</tr>
<tr>
<td></td>
<td>Prednisone 1-2 mg/kg/day if hypophysitis(^l); Prednisone 2 mg/kg/day if transverse myelitis(^k)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Considering holding if dermatologic, rheumatologic, or lymphopenia; Hold for all others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Clobetasol diproneal 0.05% or equivalent; \(^b\) Cetirizine, hydroxyzine, or equivalent; \(^c\) Avoid for Clostridium difficile; \(^d\) Levothyroxine 1.6 mcg/kg or 25-50 mcg in elderly; \(^e\) Atenolol 25-50 mg; \(^f\) Thyroid, testosterone, estrogen; \(^g\) Acetaminophen or nonsteroidal anti-inflammatory drugs; \(^h\) Consider starting at 1 mg/kg/day if gastrointestinal; \(^i\) Consider infliximab, MMF, tacrolimus, or loperamide through Grade 4; \(^j\) Infliximab-refractory is noted if no response is seen in 2 days; \(^k\) Intravenous immunoglobulin or plasmapheresis is strongly recommended; \(^l\) Gabapentin, pregabalin, or equivalent if neuropathic-related; ATG: Antithymocyte globulin, GABA: Gamma-aminobutyric acid.

## General Management of Adverse Events

<table>
<thead>
<tr>
<th>irAE</th>
<th>ICI therapy</th>
<th>Immunosuppressants</th>
<th>Other treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Discontinue if hepatitis, renal, ocular, neurologic, cardiovascular, rheumatologic, and/or hematologic; Hold for all others</td>
<td>Prednisone 1-2 mg/kg/day if peripheral neuropathy or Guillain-Barre syndrome; Consider plasmapheresis, intravenous immunoglobulin therapy, methotrexate, azathioprine, or mycophenolate mofetil through Grade 4 if myositis; Consider methotrexate or tocilizumab through Grade 4 if rituximab or cyclophosphamide if acquired hemophilia</td>
<td>In addition to the above, consider: Adding omalizumab, GABA agonists if pruritis; Plasma exchange or immunoglobulin if neurologic deficits; Pyridostigmine if myasthenia gravis; Antirheumatic drugs, methotrexate, infliximab or tocilizumab if refractory arthritis or polymyalgia-like syndrome; Infliximab, mycophenolate mofetil, intravenous immunoglobulin if pulmonary or renal; Rituximab if autoimmune encephalopathy; infliximab if cardiovascular</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue</td>
<td>Prednisone 2-4 mg/kg/day</td>
<td>In addition to the above, consider: Adding mycophenolate mofetil if hepatitis; empiric antivirals if aseptic meningitis and/or encephalitis; rituximab if acquired TTP; rituximab or cyclophosphamide if acquired hemophilia; rituximab, intravenous immunoglobulin, cyclosporine A, or mycophenolate mofetil if autoimmune hemolytic anemia; eculizumab if hemolytic uremic syndrome; intravenous immunoglobulin, rituximab, or thrombopoietin receptor agonists if immune thrombocytopenia</td>
</tr>
</tbody>
</table>

m. Pyridostigmine 30 mg three times a day; n. Sulfasalazine, methotrexate, leflunomide; o. High-dose prednisone for myocarditis; p. Avoid infliximab for hepatitis; q. Intravenous acyclovir; r. Prednisone 1 g intravenously for TTP; s. Eculizumab 900 mg weekly for four doses, 1200 mg week 5, then 1200 mg every 2 weeks. ATG: Antithymocyte globulin, GABA: Gamma-aminobutyric acid, TTP: Thrombotic thrombocytopenic purpura, ICI: Immune checkpoint inhibitor, MMF: Mycophenolate mofetil
Patient education is important
Monitor new side effects
Dose adjustments are not recommended after restarting therapy following toxicity

Toxicity of CAR-T Cells

- Neurologic toxicity: confusion, delirium, aphasia, seizures
- Anaphylaxis
- Cytokine release syndrome

# Grading and Management of Cytokine Release Syndrome

<table>
<thead>
<tr>
<th>ASBMT CRS CRS Grade</th>
<th>Defining Features of Grade</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Fever with temperature $\geq 38^\circ C$ but no hypotension or hypoxia</td>
<td>- Antipyretics and IV hydration&lt;br&gt;- Diagnostic work-up to rule out infection&lt;br&gt;- Consider growth factors and antibiotics if neutropenic</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula</td>
<td>- Supportive care as in grade 1&lt;br&gt;- IV fluid boluses and/or supplemental oxygen&lt;br&gt;- Tocilizumab +/- dexamethasone or its equivalent of methylprednisolone</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Fever with hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask, or venturi mask</td>
<td>- Supportive care as in grade 1&lt;br&gt;- Consider monitoring in intensive care unit&lt;br&gt;- Vasopressor support and/or supplemental oxygen&lt;br&gt;- Tocilizumab + dexamethasone 10-20 mg IV q 6 hrs or its equivalent of methylprednisolone</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)</td>
<td>- Supportive care as in grade 1&lt;br&gt;- Monitoring in intensive care unit&lt;br&gt;- Vasopressor support and/or supplemental oxygen via positive pressure ventilation&lt;br&gt;- Tocilizumab + methylprednisolone 1000 mg/day</td>
</tr>
</tbody>
</table>

Grading and Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

<table>
<thead>
<tr>
<th>ASBMT ICANS Grade</th>
<th>Defining Features of Grade</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>• ICE score 7-9 and/or depressed level of consciousness but awakens spontaneously</td>
<td>• Aspiration precautions and IV hydration</td>
</tr>
<tr>
<td></td>
<td>• No seizures, motor weakness, or raised ICP/cerebral edema</td>
<td>• Seizure prophylaxis with levetiracetam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EEG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Imaging of brain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Consider tocilizumab if there is concurrent CRS</td>
</tr>
<tr>
<td>Grade 2</td>
<td>• ICE score 3-6 and/or depressed level of consciousness but awakens to voice.</td>
<td>• Supportive care as in grade 1</td>
</tr>
<tr>
<td></td>
<td>• No seizures, motor weakness, or raised ICP/cerebral edema</td>
<td>• Consider dexamethasone or its equivalent of methylprednisolone</td>
</tr>
<tr>
<td>Grade 3</td>
<td>• ICE score 0-2 and/or depressed level of consciousness but awakens to tactile stimulus</td>
<td>• Supportive care as in grade 1</td>
</tr>
<tr>
<td></td>
<td>• Any clinical seizure focal or generalized that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention</td>
<td>• Dexamethasone 10-20 mg IV q 6 hours or its equivalent of methylprednisolone</td>
</tr>
<tr>
<td></td>
<td>• No motor weakness</td>
<td>• Control seizures with benzodiazepines (for short-term control) and levetiracetam +/– phenobarbital and/or lacosamide</td>
</tr>
<tr>
<td></td>
<td>• Focal/local edema on neuroimaging</td>
<td>• High-dose methylprednisolone 1000 mg/day for focal/local edema</td>
</tr>
<tr>
<td>Grade 4</td>
<td>• ICE score 0 and patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma</td>
<td>• Supportive care as in grade 1</td>
</tr>
<tr>
<td></td>
<td>• Life-threatening prolonged seizure (&gt;5 min); or repetitive clinical or electrical seizures without return to baseline in between</td>
<td>• High-dose methylprednisolone 1000 mg/day</td>
</tr>
<tr>
<td></td>
<td>• Deep focal motor weakness such as hemiparesis or paraparesis</td>
<td>• Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide</td>
</tr>
<tr>
<td></td>
<td>• Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing’s triad</td>
<td>• Imaging of spine for focal motor weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lower ICP by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema</td>
</tr>
</tbody>
</table>

Abbreviations: ASBMT: American Society for Bone Marrow Transplant; CRS, cytokine release syndrome; EEG: electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE: Immune effector Cell-associated Encephalopathy; ICP: intracranial pressure; IV, intravenous.
Among the latest innovations in cancer therapies are immuno-oncology agents: these include immune checkpoint inhibitors (antibodies) aimed at CTLA-4 and PD-1/L1 and CAR-T therapies. These agents have demonstrated promise in the treatment of several tumor types, with findings often characterized by extended OS in the long-term. There are now a number of biomarkers being assessed to predict response to specific IO therapies. Activation of the immune system against tumors can result in a novel spectrum of irAEs with checkpoint inhibitors and CAR-T therapies.
Medical and Pharmacy Management Strategies to Enhance Outcomes Requiring Treatment with Immuno-Oncology Agents
Cost for Cancer Care Continue to Rise

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval - 1965-2019

Current and Potential Future Use of Endpoints in Health Technology Assessment of Oncology Drugs

**Where median OS expected**

- Overall survival
  - Preferred criterion for HTA
    - Preferred criterion for HTA
    - Surrogate endpoints considered

**Where median OS is not a desirable primary endpoint within trial timelines**

- Surrogate endpoints
  - Not routinely accepted
    - Surrogate endpoints validated for relevant disease state considered

- HRQoL
  - Viewed as supportive in some countries, but interpretation not widely understood
    - Increasingly important, but need to establish the MCID in relevant setting
      - Use to support PFS and demonstrate that PFS gain is meaningful to patients

- HRQoL, health-related quality of life
- HTA, health technology assessment
- MCID, minimal clinically important difference
- OS, overall survival
- PFS, progression-free survival

How Do Payers Approach Value?

\[ V = \frac{\text{Benefit}}{\text{Cost}} \]

- Clinical Value
- Cost of Delivering New Technology
- Costs Averted
null
Current and Future Provider Use of Value Frameworks

“Is your practice currently using any of these oncology value frameworks? Do you see value frameworks playing a greater role in career patient care decisions?”

- Current use of VFs:
  - 58% do not use
  - 42% consider, but not influential

- Anticipated future use of VFs:
  - 33% do not use
  - 67% influential use

Type of use:
- Red: Do not use
- Orange: Consider, but not influential
- Green: Influential use

Current use and anticipated growth in future use of VFs driven by providers’ perception of the growing importance of VFs to payers.

VF = value framework.
Available Oncology Value Frameworks

- American Society of Clinical Oncology (ASCO) Value Framework
- National Comprehensive Cancer Network (NCCN) Evidence Blocks
- Memorial Sloan Kettering Cancer Center Drug Abacus
- Institute for Clinical and Economic Review (ICER) Value Assessment Framework
- European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale

Which Oncology Value Framework uses a “Net Health Benefit Score” as its primary outcome?

1. American Society of Clinical Oncology (ASCO) Value Framework
2. European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale
3. Institute for Clinical and Economic Review (ICER) Value Assessment Framework
4. Memorial Sloan Kettering Cancer Center Drug Abacus
5. National Comprehensive Cancer Network (NCCN) Evidence Blocks
6. None of the above
<table>
<thead>
<tr>
<th>Emphasis</th>
<th>ASCO</th>
<th>NCCN</th>
<th>MSKCC</th>
<th>ICER</th>
<th>ESMO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target stakeholder</td>
<td>Patient Physician</td>
<td>Patient Physician</td>
<td>Physician Policymaker</td>
<td>Payer Policymaker</td>
<td>Payer Policymaker</td>
</tr>
<tr>
<td>Conditions addressed</td>
<td>Oncology: solid, blood</td>
<td>Oncology: solid, blood, radiology, surgery</td>
<td>Oncology: solid, blood</td>
<td>All conditions, focus on new drugs of high impact</td>
<td>Oncology: solid, blood, radiology, surgery</td>
</tr>
<tr>
<td><strong>Clinical trial data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breadth of evidence</td>
<td>1 trial, RCT</td>
<td>Published data, panel members’ clinical experience, case reports</td>
<td>1 trial, registration trial of first indication (FDA label)</td>
<td>RCT meta-analysis and manufacturer-provided data</td>
<td>1 trial, RCT, comparative outcomes study, meta-analysis</td>
</tr>
<tr>
<td>Trial sample size accounted</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Indirectly, through lower bound of 95% CI</td>
</tr>
<tr>
<td>Allows for single-arm trials</td>
<td>Partially</td>
<td>Likely</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Acknowledges trial contamination</td>
<td>No</td>
<td>Likely</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Accounts for patient preference</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net health benefit score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence Blocks score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DrugAbacus price</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness; budget impact</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESMO MCBS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cost/price</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price (WAC or ASP+) per month or course of therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affordability scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacus price per month or course of therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not specified, left to payers to evaluate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASCO indicates American Society of Clinical Oncology; ASP, average sales price; CI, confidence interval; ESMO, European Society for Medical Oncology; FDA, US Food and Drug Administration; ICER, Institute for Clinical and Economic Review; MCBS, Magnitude of Clinical Benefit Scale; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; RCT, randomized controlled trial; WAC, wholesale acquisition cost.

## Inputs of Various Oncology Value Frameworks

<table>
<thead>
<tr>
<th>Input</th>
<th>ASCO 2.0</th>
<th>NCCN</th>
<th>MSKCC</th>
<th>ICER</th>
<th>ESMO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td>Advanced disease: HR (death), OS, PFS, response rate</td>
<td>Vary, dependent on indication</td>
<td>Improvement in OS or surrogate endpoint</td>
<td>Vary, dependent on indication</td>
<td>Advanced disease: OS, PFS, palliation of symptoms, response rate</td>
</tr>
<tr>
<td>Adjuvant therapy: HR (death), OS, DFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety/toxicity</td>
<td>Based on side-effect frequency, grade</td>
<td>Effect on daily life</td>
<td>Grade 3/4: probability of discontinuing</td>
<td>Severe side effects</td>
<td>Grade 3/4; severe side effects</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-free interval</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Tail of the curve</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Quality of life/palliation</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Patient preferences</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Epidemiologic factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease burden/incidence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Unmet need</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>R&amp;D factor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novelty</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Research cost</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug Costs</td>
<td>Advanced disease: drug acquisition cost per month</td>
<td>Total treatment cost</td>
<td>ASP/AWP</td>
<td>Total cost per person, total cost to payers</td>
<td>Not specific, left to payers to evaluate</td>
</tr>
<tr>
<td>Adjuvant therapy: drug acquisition cost/entire treatment regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost to healthcare system</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
### Scoring Algorithms of Various Oncology Value Frameworks

<table>
<thead>
<tr>
<th>ASCO</th>
<th>NCCN</th>
<th>MSKCC</th>
<th>ICER</th>
<th>ESMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulaic</td>
<td>Expert-based</td>
<td>Formulaic</td>
<td>Formulaic and expert-based</td>
<td>Formulaic</td>
</tr>
</tbody>
</table>

## Outputs of Various Oncology Value Frameworks

<table>
<thead>
<tr>
<th>Output</th>
<th>ASCO</th>
<th>NCCN</th>
<th>MSKCC</th>
<th>ICER</th>
<th>ESMO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health benefit</strong></td>
<td></td>
<td>Score (1-5) for each of 5 key measures displayed as evidence blocks</td>
<td>No</td>
<td>Assessment of care value (high/intermediate/low)</td>
<td>A relative ranking of the magnitude of clinically meaningful benefit</td>
</tr>
<tr>
<td><strong>Cost readout</strong></td>
<td></td>
<td>Reported as relative affordability, considers overall cost of intervention (eg. cost of drug, infusions, supportive care management)</td>
<td>DrugAbacus value-based price per month or course of therapy: a user-generated value assessment directly compared with reported Medicare payment limit, 106% ASP</td>
<td>Cost per year; cost-effectiveness of drug, with recommendations on what drug price should be to be cost-effective</td>
<td>Not specified; left to payers to evaluate</td>
</tr>
<tr>
<td><strong>Drug cost, relative or absolute value</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cost to patient</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cost to healthcare system</strong></td>
<td>No</td>
<td>Total drug and medical costs</td>
<td>Rarity per budget impact</td>
<td>Incremental cost-effectiveness ratio and budget impact</td>
<td>No</td>
</tr>
</tbody>
</table>

These Value Frameworks Lend Insight to Payer-led Management Interventions


<table>
<thead>
<tr>
<th>Clinical Pathways</th>
<th>Step Edits</th>
<th>Formulary Positioning</th>
</tr>
</thead>
</table>

**Score for individual agents or regimens based on efficacy, safety, and cost**
Value Frameworks May Not Be Adequately Calibrated for the Assessment of IO Agents

- 23 metastatic indications for 6 immuno-oncology agents were approved by the FDA from March 2011 to August 2017
  - 10 (43%) of the approvals were based on survival end points, while 13 (57%) were based on response rates
- Only 3 drug indications fulfilled the threshold defined for the survival rate of patients receiving standard care (minimum 20%) in the ASCO framework
- 9 indications achieved the required level of improvement in proportion to patients alive in the test regimen compared with the standard (above 50%)
- There was overlap between these 2 criteria for 3 drug indications, allowing them to gain the durable survival bonus points awarded by the ASCO framework
- Durable survival and response rates of modern immuno-oncology agents are rarely recognized as significant by current oncology value frameworks
  - This may be due to insufficient demonstration of efficacy of such agents or inappropriately calibrated value frameworks

A Thorough Understanding of Appropriate Outcomes Measures is Necessary Due to Emerging Specialty Drug Contracting Models

45% of private payers were involved in pay-for-performance and risk-sharing programs in 2010; the number rose to 62% in 2013, and usage of these programs was estimated to be as high as 75% in 2016

Cost Effectiveness Analysis is Not Yet Fully Accepted in Health Care Decision Making

• Most payers do not explicitly use comparative effectiveness analysis or other sophisticated tools
• Not generally accepted in the US for making healthcare decisions

“In the modern American political system, for a policy option to successfully navigate the path from a bill to a law often requires widespread public appeal, or at least little public opposition. This study should offer a warning to the research community that, despite the cost-saving potential of CER, it is likely to engender widespread opposition when put into practice in the United States—particularly if decisions are widely known by the public.”

Impact of COVID-19 on Managing Patients Receiving Immunotherapy

People with cancer who contract COVID-19 appear to have a greater risk for severe COVID-19 illness and death, but this may depend on their cancer stage and the type of treatment they are receiving.¹

Proactive strategies are needed to reduce likelihood of infection as well as improve early identification.¹

Patients receiving immunotherapy for thoracic cancer are at higher risk for serious events from COVID-19.²

Serious consideration need to be taken when making decisions regarding patient selection for therapy, duration of therapy and the decision to combine immunotherapy with cytotoxic chemotherapy in thoracic cancer patients.²

HCPs need to develop strategies that minimize potential COVID-19 exposure as well as re-evaluate therapies for the most vulnerable cancer populations. However life saving cancer treatments should not be stopped.¹

Value frameworks are not going to go away
Methods and approaches may be internalized by payers
Nongovernment payers will not be transparent unless compelled to be so
Government payers will be transparent but will avoid CEA and related tools for some time
ICER and other nonpayer/nongovernment organizations will play a role by engaging in a public discourse
This roll for these nongovernmental-HTA organizations will require them to be more inclusive of various stakeholders, and more transparent in methods and discussion
Cancer treatments should not be stopped. HCPs need to develop strategies that minimize potential COVID-19 exposure as well as examine therapies for the most vulnerable cancer populations.
Faculty Idea Exchange and Q&A Session

Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Yung Lyou, MD, PhD
Medical Oncologist
Assistant Clinical Professor
Department of Medical Oncology
City of Hope
**Option 1:** Complete the online post-survey and evaluation form immediately following the virtual symposium. The link to the survey will appear on your screen at the conclusion of the webcast. If you are unable to fill out the evaluation immediately following the virtual symposium, please note that a personalized evaluation link will be emailed to you following the virtual symposium at the account you registered with. Once you fill out your evaluation, your certificate will be emailed to you. **For Pharmacists,** in order to submit your credit to the CPE Monitor:

Please go to [www.impactedu.net/cpe](http://www.impactedu.net/cpe)
Enter code: **0615**
You will then need to log in or create an account ensuring your NABP and DOB information is entered and correct. Be sure to enter today’s date, **June 15, 2020,** as the date of participation. You will be immediately notified if your submission has been accepted or if there are any issues. Once accepted, the record of your participation will appear in the CPE Monitor within 48 hours. **Credit must be uploaded to CPE Monitor within 30 days.**

**Option 2:** Print the ‘Fax Evaluation Form’ in the Handouts section and turn in the completed version via fax or email to the number or email address located at the top of the form. A certificate will be emailed to you within 3-4 weeks. **For Pharmacists:** upon receipt of the completed evaluation form, you will receive an email within 3 weeks with a link and directions to submit your credit to the NABP CPE Monitor Service. **Pharmacists have up to 30 days to complete the evaluation and claim credit for participation so that information can be submitted to CPE Monitor as required.**
ECONOMIC AND CLINICAL OUTCOMES ASSESSMENT OF IMMUNO-ONCOLOGY AGENTS

A Guide for Payer Decision Makers

Live Webcast
Monday, June 15, 2020
12:30 PM – 2:00 PM ET