THE IMMUNO-ONCOLOGY TRANSFORMATION: Implications for Managed Care

Jointly provided by

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Live Webcast
Welcome

Jeffrey D. Dunn, PharmD, MBA
Vice President
Clinical Strategy and Program and Industry Relations
Magellan Rx Management
<table>
<thead>
<tr>
<th>Agenda</th>
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</table>
| **Pre-Activity Learning Assessment and Opening Comments/Overview**  
**Jeffrey Dunn, PharmD, MBA** |
| *Assessing the Clinical Benefits and Appropriate Use of Immuno-Oncology Agents*  
**Joan H. Schiller, MD** |
| *Medical and Pharmacy Benefit Design Strategies for Immuno-Oncology Agents*  
**Jeffrey Dunn, PharmD, MBA** |
| *Health Plan Strategies to Enhance Patient Outcomes with Immuno-Oncology Agents*  
**John Fox, MD, MHA** |
| Audience Q&A Session |
| Key Takeaways and Closing Comments; Post-Activity Assessment and Evaluation |
| Adjournment |
Learning Objectives

• Characterize the role of the immune system in immunosurveillance and elimination of malignant cell lines with respect to cancer immunoediting
• Describe 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 characterize the importance of cumulative assessment of outcomes
• Apply comprehensive analyses of clinical trial data pertaining to recently approved and investigational PD-1/PD-L1 inhibitors and CAR-T therapies
• Characterize the incongruent application of traditional payer cost-sharing and benefit design approaches to the management of innovative immuno-oncology agents
• Evaluate current and proposed payer initiatives for the funding and management of PD-1/PD-L1 inhibitors and CAR-T therapies
Assessing the Clinical Benefits and Appropriate Use of Immuno-Oncology Agents

Joan H. Schiller, MD
Professor
University of Virginia
Tumor-associated antigens can trigger a tumor-specific immune cell response:

1. **Tumors** express a multitude of proteins, known as **tumor-associated antigens**\(^1,2,3,4\)

2. **Antigen presenting cell (APC)** captures **tumor-associated antigens**\(^2\)

3. **Activated APC** can interact with T cells\(^4\)

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**T-cell activation: cytotoxic T cells**


4. **Activated APC** presents the **tumor-associated antigen** to the T cell along with a **co-stimulatory signal**

5. **Cytotoxic T cell** induces **apoptosis** in **tumor** cell

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Inactive T cell activates T cells, which proliferate. Activated APC presents the tumor-associated antigen to the T cell along with a co-stimulatory signal. Activated T cell activates APR and induces apoptosis in the tumor cell.
How Does T-Cell Activation Happen?

Activated T Cells → Recognize Tumor Associated Antigens on Tumor Cells

**CTLA4**: Cytotoxic T lymphocyte antigen 4  
**PD-1**: Programmed death 1  
**PD-L1**: PD ligand 1

**Lymph Nodes**: Dendritic cell

**Tumor**: T cell

**Priming phase**: MHC-TCR, Activation signal

**Effector phase**: MHC-TCR, Inhibitory signal

**Cytokines**
Turning It Off…. Need to dampen down the immune system to keep it from running wild and to prevent autoimmune diseases.

**CTLA4:** Cytotoxic T lymphocyte antigen 4  
**PD-1:** Programmed death 1  
**PD-L1:** PD ligand 1  

So What Goes Wrong? CTLA-4 and PD-1/PD-L1 Inhibit Anti-tumor Immune Responses by
-- Preventing Activation of the T Cells (CTL-4) AND/OR
---Preventing Recognition of the Tumor cell

**CTLA4**: Cytotoxic T lymphocyte antigen 4
**PD-1**: Programmed death 1
**PD-L1**: PD ligand 1

---

**Lymph Nodes**

**Tumor**

---

So What to Do?
Inhibit CTLA4 (Ipilimumab)
OR Inhibit PD1 or PDL1

**CTLA4**: Cytotoxic T lymphocyte antigen 4
**PD-1**: Programmed death 1
**PD-L1**: PD ligand 1

Cytokines

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### Available Immune Checkpoint Inhibitors

<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>Anti–PD-1</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Anti–PD-1</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td>Anti–PD-1</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Anti–PD-L1</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Anti–PD-L1</td>
</tr>
<tr>
<td>Durvalumab</td>
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</table>

Metastatic Melanoma – Overall Survival

Chemotherapy

Ipilimumab


No. at Risk

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Chemotherapy</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>108</td>
<td>1861</td>
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<tr>
<td>24</td>
<td>96</td>
<td>839</td>
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<td>60</td>
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<td>72</td>
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<td>170</td>
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<td>84</td>
<td>28</td>
<td>53</td>
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<td>96</td>
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<tr>
<td>108</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>120</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Median OS: 11.4 mo (95% CI: 10.7-12.1)

3-yr OS rate: 22% (95% CI: 0.32-0.92)
Pembrolizumab vs. Ipilimumab in Advanced Melanoma: Keynote-006

Nivolumab vs. Ipilimumab in Resected Stage III/IV Melanoma: CheckMate-238


<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events/patients</td>
<td>154/453</td>
<td>206/453</td>
</tr>
<tr>
<td>Median (95% CI)</td>
<td>NR</td>
<td>NR (16.6, NR)</td>
</tr>
<tr>
<td>HR (97.5% CI)</td>
<td>0.65 (0.51, 0.83)</td>
<td></td>
</tr>
<tr>
<td>Long-rank <em>P</em></td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
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<tbody>
<tr>
<td>0-3</td>
<td>453</td>
<td>453</td>
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<tr>
<td>3-6</td>
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<td>6-9</td>
<td>353</td>
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<tr>
<td>71-100</td>
<td>0</td>
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</table>

Long Term Survival at 2 years in OAK Trial: Atezolizumab vs Docetaxel in 2nd line+ NSCLC

Locally Advanced or Metastatic NSCLC
- 1-2 prior lines of chemo including at least 1 platinum-based
- Any PD-L1 status

R: 1:1

Atezolizumab 1200 mg IV q3w → PD or loss of clinical benefit → Non-Protocol Therapy (NPT) / Survival Follow-up

Docetaxel 75 mg/m2 q3w → PD → NPT / Survival Follow-up No crossover to atezolizumab

2-year OS Rates
- Atezolizumab: 31%
- Docetaxel: 21%

No. of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>425</td>
<td>425</td>
<td>425</td>
</tr>
<tr>
<td>363</td>
<td>336</td>
<td>263</td>
</tr>
<tr>
<td>305</td>
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<td>248</td>
<td>218</td>
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<td>218</td>
<td>188</td>
<td>151</td>
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<td>188</td>
<td>157</td>
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<td>136</td>
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<td>71</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>27</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>
Phase 3 Trial of Chemo + Pembrolizumab or Chemo Alone for Previously Untreated NSCLC: Keynote-189

Overall Survival, ITT

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro/Pem/Plat</td>
<td>31.0%</td>
<td>0.49</td>
</tr>
<tr>
<td>Placebo/Pem/Plat</td>
<td>52.4%</td>
<td>(0.38-0.64)</td>
</tr>
</tbody>
</table>

Median (96% CI)
NR (NE-NE)
11.3 mo (8.7-15.1)

Data cutoff date: Nov 8, 2017

Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Paper presented at: American Association for Cancer Research Annual Meeting; April 14-18, 2018; Chicago, IL.
PD-L1 TPS Predicts PFS: Keynote-189

Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Paper presented at: American Association for Cancer Research Annual Meeting; April 14-18, 2018; Chicago, IL.
**Pembrolizumab vs Chemo in 1st Line NSCLC**

**KEYNOTE-024 Study Design (NCT02142738)**

**Key Eligibility Criteria**
- Untreated stage IV NSCLC
- PD-L1 TP S ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

**R (1:1) N = 305**

- **Pembrolizumab**
  - 200 mg IV Q3W (2 years)

- **Platinum-Doublet Chemotherapy**
  - 4-6 cycles

**Key End Points**
- Primary: PFS (RECIST v1.1 per blinded, independent central review)
- Secondary: OS, ORR, safety
- Exploratory: DOR

- Carbo + pemetrexed*
- Cis + pemetrexed*
- Carbo + gemcitabine
- Cis + gemcitabine
- Carbo + paclitaxel

*Reck, et al; NEJM 2016*
Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Events, n</th>
<th>Median, mo</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>44</td>
<td>NR</td>
<td>0.60</td>
<td>0.005</td>
</tr>
<tr>
<td>Chemo</td>
<td>64</td>
<td>NR</td>
<td>0.41-0.89</td>
<td></td>
</tr>
</tbody>
</table>

Data cut-off: May 9, 2016

CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥10 mut/Mb)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Nivo + ipi (n = 139)</th>
<th>Chemo (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, b mo</td>
<td>7.2</td>
<td>5.4</td>
</tr>
<tr>
<td>HR(^c)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>97.5% CI</td>
<td>0.41, 0.81</td>
<td></td>
</tr>
<tr>
<td>(P = 0.0002)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- In patients with TMB <10 mut/Mb treated with nivo + ipi vs chemo, the HR was 1.07 (95% CI: 0.84, 1.35)\(^d\)
Responses Observed in TMB ≥10 mut/Mb Regardless of Tumor PD-L1 Expression


- **ORR for all treated patients:** 41% in PD-L1 ≥1% subgroup (n=138) and 15% in PD-L1 <1% subgroup.  
- **bCR=0; cCR=16%; dCR=4%; eCR=4%**

**PD-L1 <1%**
- TMB <10 mut/Mb: 5/22
- TMB ≥10 mut/Mb: 9/19

**PD-L1 ≥1%**
- TMB <10 mut/Mb: 18/28
- TMB ≥10 mut/Mb: 42/26

\(^a\)ORR for all treated patients: 41% in PD-L1 ≥1% subgroup (n=138) and 15% in PD-L1 <1% subgroup 114; \(^b\)CR=0; \(^c\)CR=16%; \(^d\)CR=4%; \(^e\)CR=4%
Predicting Response: Neoantigens and Related Biomarkers

• Neoantigens
  • Tumors with a high burden of neoantigens have been shown to be more sensitive to immunotherapy
  • Being investigated in anti-CTLA-4 and anti-PD-1 therapy

• Tumor Mutational Burden (TMB)
  • May potentially be used as a surrogate to indirectly assess neoantigen load

• Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) status
  • May potentially be used as a surrogate to indirectly assess neoantigen load

• Tumor Microenvironment

“Hot” or “inflamed” tumors due to immune recognition

• High infiltration of CD8+ Tumor Infiltrating Lymphocytes (TILs)
• Presence of chemokines
• Type 1 interferon
• Melanoma and other tumor types
Predicting response to Checkpoint inhibitors
Tumor microenvironment

MA11.06 - Prognostic Value of Complement System in NSCLC and its Association with PD-1 and PD-L1 Expression (Now Available)
11:05 - 11:10  | Presenting Author(s): Luis M Montuenga  | Author(s): Daniel Ajona, María José Pajares, Javier Freire, Javier Gomez-Roman, Elena Martinez-Terroba, Sergio Ortiz-Espinosa, Ana Lledo, Elisabeth Arenas-Lazaro, Jackeline Agorreta, Fernando Lecanda, Ruben Pio

MA11.07 - Expression of LAG-3 and NY-ESO-1 In Tumor Cells is Promising Biomarker Predicting Durable Clinical Benefit of PD-1 Blockade in Advanced NSCLC (Now Available)
11:10 - 11:15  | Presenting Author(s): Hee Ryeong Jang  | Author(s): Se Hyun Kim, Kyoung Jin Suh, Yu Jung Kim, Mi So Kim, Bhumsuk Keam, Tae Min Kim, Jin-Haeng Chung, Dong-Wan Kim, Dae Seog Heo, Jong-Seok Lee

MA11.08 - Discussant - MA 11.05, MA 11.06, MA 11.07 (Now Available)
11:15 - 11:30  | Presenting Author(s): Erin Schenk

MA11.09 - Single-Cell Characterization of the Immunologic Microenvironment in Advanced-Stage, Oncogene-Driven NSCLC (Now Available)
11:30 - 11:35  | Presenting Author(s): Julia Rotow  | Author(s): Caroline McCoach, Ashley Maynard, David Naeger, Yaron Gesthalter, K Pallav Kolli, Spyros Darmanis, Trever G Bivona, Collin Blakely, Jonathan Weissman

MA11.10 - Identification of Mismatch Repair Deficient Lung Adenocarcinomas Using Targeted Next-Generation Sequencing (Now Available)
11:35 - 11:40  | Presenting Author(s): Navin Rajput Mahadevan  | Author(s): Priyanka Shivadasani, Jonathan Nowak, Mark
Immune-Related Adverse Events (IRAEs)

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

Occasional (5%-20%) IRAEs

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis
  - Macropapular/pruritus
- Pneumonitis
- Hepatitis
- Pancreatitis
- Arthritis
- Neuropathies

YERVOY immune-related adverse reactions management guide. October 2012.
Safety and Tolerability of Therapy with Checkpoint Inhibitors

- Spectrum of observed toxicities:
  - GI: diarrhea and colitis
  - Pulmonary: pneumonitis (challenges in diagnosis)
  - Dermatologic: rash and pruritus
  - Hepatic toxicity (importance of plasma screening)
  - Endocrine: hypophysitis, hypothyroidism (importance of plasma screening)

- Timing for appearance of toxicities

- Fraction of patients with toxicities: Anti-PD-1 versus combined anti-PD-1 and anti-CTLA-4
Pembrolizumab vs Chemo in 1st Line NSCLC

Treatment-Related AEs With Incidence >10%

Grade
1-2
3-4
Pembrolizumab
Chemotherapy

Immune-Mediated AEs With Pembrolizumab

Overall incidence
- 29% any grade
- 10% grade 3-4
- No grade 5 events

Data cut-off: May 9, 2016.
All Providers Must Be Vigilant in Recognizing Diverse Toxicities

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis

- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor & sensory neuropathies
- Arthritis

• Less common: hematologic; cardiovascular; ocular, renal

Lipson, ASCO 2014
IRAEs May Require Weeks of High Dose Steroids and Complex Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>• Supportive care +/- hold drug</td>
</tr>
</tbody>
</table>
| Grade 2 | • Hold drug  
|         | • Re-dose at lower dose once toxicity resolved to <= Grade 1  
|         | • Low dose steroids if symptoms do not resolve in 1 week |
| Grade 3/4 | • D/C drug  
|           | • R/o other etiologies  
|          | • Consider empiric antibiotics, biopsy  
|          | • High dose steroids  
|          | • Taper over >= 1 month until toxicity resolves to <= Grade 1 |
Even Low Grade IRAEs Cannot Be Ignored

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>• Supportive care +/- hold drug</td>
</tr>
</tbody>
</table>
| Grade 2 | • Hold drug  
• Re-dose at lower dose once toxicity resolved to \(\leq\) Grade 1  
• Low dose steroids if symptoms do not resolve in 1 week |
| Grade 3/4 | • D/C drug  
• R/o other etiologies  
• Consider empiric antibiotics, biopsy  
• High dose steroids  
• Taper over \(\geq\) 1 month until toxicity resolves to \(\leq\) Grade 1 |
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 (CAR) T-Cell Therapy

1. T cells are collected from the patient’s blood.
2. In the laboratory, the chimeric antigen receptor (CAR) is added to the patient’s T cells.
3. The CAR T cells are infused into the patient.

IN THE BODY
CAR T cells recognize the patient’s cancer cells.
CAR T cells kill the patient’s cancer cells.
CAR T cells multiply.
Axicabtagene Ciloleucel in Refractory Aggressive Non-Hodgkin Lymphoma (NHL)

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

**ZUMA-1 (axicabtagene ciloleucel)**

**SCHOLAR-1 (traditional salvage therapies)**

• Neurologic toxicity: confusion, delirium, aphasia, seizures

• Anaphylaxis

• Cytokine release syndrome

Characterizing the Manifestations of Cytokine Release Syndrome (CRS) Across Various Organ Systems

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea, hypoxemia</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Elevated D-dimer, hypofibrinogenemia ± bleeding</td>
</tr>
<tr>
<td>Renal</td>
<td>Azotemia</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Transaminitis, hyperbilirubinemia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dysmetria, altered gait, seizures</td>
</tr>
</tbody>
</table>

Multiple mechanisms that limit autoimmunity need to be overcome in cancer immunotherapy.
Future Promise in Combination I-O Therapy

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, such as cytotoxic T cells and NK cells.

Among the latest innovations in cancer therapies are immuno-oncology agents: these 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.

Activation of the immune system against tumors can result in a novel spectrum of IRAEs with checkpoint inhibitors and CARs/NEs with CAR-T therapies.

Combination regimens offer further potential for future regimens, with a number of biomarkers being assessed to predict response to specific I-O therapies.
PD-1/L1 Antagonist Activity Across Tumor Types

**Active**
- Melanoma
- Renal cancer (clear cell)
- NSCLC – adenocarcinoma and squamous cell
- Head and neck cancer
- Urothelial (bladder) cancer
- Merkel Cell
- Mismatch repair deficient tumors
- Hodgkin Lymphoma
- Hepatocellular carcinoma
- Gastric and GE junction
- Cervical cancer
- PMBCL

**Minimal to no activity**
- Anal cancer
- Squamous Cell Ca of Skin
- Small cell lung cancer
- Triple negative breast cancer
- Ovarian cancer
- Thymic carcinoma
- Mesothelioma
- Diffuse large cell lymphoma
- Follicular lymphoma
- Prostate cancer
- MMR+ Colon cancer
- Myeloma
- Pancreatic Cancer
- ER+ breast cancer

**Is the Cost Sustainable??**
Medical and Pharmacy Benefit Design Strategies for Immuno-Oncology Agents

Jeffrey Dunn, PharmD, MBA
Vice President, Clinical Strategy and Programs and Industry Relations
Magellan Rx Management
Oncology Led All Classes of Drugs in Terms of Trend in 2018 with a Sizeable Specialty Component

<table>
<thead>
<tr>
<th>THERAPY CLASS</th>
<th>PMPY SPEND</th>
<th>TRENDS</th>
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</thead>
<tbody>
<tr>
<td>Inflammatory conditions</td>
<td>$140</td>
<td>14.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$80</td>
<td>4.1%</td>
</tr>
<tr>
<td>Oncology</td>
<td>$120</td>
<td>18.1%</td>
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<tr>
<td>Multiple Sclerosis</td>
<td>$60</td>
<td>-4.8%</td>
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<tr>
<td>HIV</td>
<td>$140</td>
<td>11.7%</td>
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<tr>
<td>Pain/Inflammation</td>
<td>$60</td>
<td>-11.1%</td>
</tr>
<tr>
<td>Attention disorders</td>
<td>$60</td>
<td>-8.2%</td>
</tr>
<tr>
<td>Asthma</td>
<td>$60</td>
<td>-7.3%</td>
</tr>
<tr>
<td>High blood pressure/heart disease</td>
<td>$60</td>
<td>-13.4%</td>
</tr>
<tr>
<td>Depression</td>
<td>$60</td>
<td>-3.8%</td>
</tr>
<tr>
<td>Skin conditions</td>
<td>$60</td>
<td>4.8%</td>
</tr>
<tr>
<td>Contraceptives</td>
<td>$60</td>
<td>-9.6%</td>
</tr>
<tr>
<td>High blood cholesterol</td>
<td>$60</td>
<td>-27.0%</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>$60</td>
<td>11.7%</td>
</tr>
<tr>
<td>Seizures</td>
<td>$60</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

2018

Traditional generic

Traditional brand

Specialty generic

Specialty brand
Spending on Oncology Therapies has Risen Consistently for Several Decades

- 73 new cancer therapies approved or indications expanded since 2012
- 16 new cancer drugs approved in 2017, all targeted therapies
- Global spending on cancer medications rose from $96 billion in 2013 to $133 billion in 2017
  - US led the trend with highest spend: 33% (2013) to 50% (2017) of global spend
- US cancer drugs expected to cost $100 billion by 2022
- Median annual cost of new cancer drug doubled in last decade from $75,000 to $150,000
- 87% of cancer drugs are used by fewer than 10,000 patients each year
- 700 new molecules in late-stage development now

New Cancer Therapies Approved/Indications Expanded

<table>
<thead>
<tr>
<th>Year</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12</td>
<td>10</td>
<td>21</td>
<td>11</td>
<td>16</td>
<td>3</td>
</tr>
</tbody>
</table>

Total US Spending Oncology Therapeutic Medicines, 2013-2017

Chart Source: IQVIA, ARK R&D Intelligence, Dec 2017; IQVIA Institute, Mar 2018, CenterWatch: FDA Approved Drugs for Oncology.
Attitudes Toward the Management of Oncology Therapies Have Long Since Changed: Cancer is No Longer Untouchable

Price and value of therapies rarely questioned

Vigorous debate about the overall value* of treatments

Payers now actively apply payment reforms and quality measurement to cancer services

*Clinical, pharmacoeconomic, humanistic, societal, etc.
## Oncology Management Strategies Willing to Implement

<table>
<thead>
<tr>
<th>% of payers (n = 45)</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>67%</td>
<td>Restricting specified regimens based on the patient’s performance status when aligned with NCCN recommendations</td>
</tr>
<tr>
<td>67%</td>
<td>Incentivizing lower cost regimes when they carry the same level of compendia recommendation</td>
</tr>
<tr>
<td>47%</td>
<td>Limiting agents that are recently approved by the FDA under an accelerated approval pathway to patients who meet the study eligibility criteria used for FDA approval</td>
</tr>
<tr>
<td>31%</td>
<td>Not covering NCCN 2A recommendations if evidence is lacking</td>
</tr>
<tr>
<td>2%</td>
<td>Other (preferring a lower cost agent but only if NCCN 1 vs. 2A or lower)</td>
</tr>
<tr>
<td>7%</td>
<td>None of the above</td>
</tr>
</tbody>
</table>

Closed formularies are becoming more common
  - NDC block until review
  - Increasing number of excluded drugs

Narrowing the number of preferred or covered products

More restrictive policies/PA criteria: going beyond the label to consider clinical trial inclusion/exclusion
  - Restricted patient population
  - Stopping rules for nonresponse
  - More rigorous re-authorization criteria
Tufts Study on Restrictive Coverage

Across 3,417 decisions addressing coverage for 302 drug indication pairs...

- 64% Covered the same way by all or most (>75%) plans
- 36% Covered differently

The majority were covered the same way...

And specifically the decisions were...

- Not covered: 5%
- More restrictive: 33%
- Consistent with FDA label: 52%
- Less restrictive: 9%

• Health plans restricted coverage of drugs indicated for cancer less often than they did coverage of drugs indicated for other diseases.

• Using multivariate regression, it was found that several drug-related factors were associated with less restrictive coverage, including indications for orphan diseases or pediatric populations, absence of safety warnings, time on the market, lack of alternatives, and expedited FDA review.

Potential Factors in Oncology Formulary Decision Making

- Payer-Determined Medical Necessity
- Cost Effectiveness
- Efficacy
- Safety
- Physician Support
- Budget Impact
- PBM, Physician, and Pharmacist Contracts
- Discounts and Rebates
- Acquisition Costs
- Disease Management Programs
- HEDIS, JCAHO, and NCQA
- Politics and Public Image
- DECISION

HEDIS = Healthcare Effectiveness Data and Information Set; JCAHO = Commission on Accreditation of Healthcare Organizations; NCQA = National Committee for Quality Assurance; PBM = pharmacy benefit manager.

• Payers are demonstrating more interest in Institute for Clinical Effectiveness Research (ICER) reviews and the potential for use of Cost Effectiveness Analysis (CER)

• Drug evaluation, contracting, etc. are contributing to large discrepancies between plan coverage and coverage policies
Use of ICER Reports by Payers

At what point were ICER reports used in the formulary decision process?

- 75% evidence source for preparing P&T recommendations
- 69% inform or validate the payer’s own analysis
- 64% used during research process
- 56% used during the P&T review phase
- 33% use during coverage policy development

May 2015 Survey of AMCP eDossier Users (N=99)

Organizations choose whether to include cost data as part of the P&T Committee Review process. If cost data is not included, drugs are reviewed solely on clinical efficacy, safety, unmet need. An administrative committee is then tasked with final formulary placement decisions based on:

- P&T Committee’s clinical evaluation
- Cost-effectiveness data
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

## Emphasis of Various Oncology Value Frameworks

<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</td>
<td>Physician</td>
<td>Patient</td>
<td>Physician</td>
<td>Payer</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>Readout</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Net health benefit score</td>
<td>Evidence Blocks score</td>
<td>DrugAbacus price</td>
<td>Cost-effectiveness; budget impact</td>
<td>ESMO MCBS</td>
</tr>
<tr>
<td>Cost/price</td>
<td>Price (WAC or ASP+) per month or course of therapy</td>
<td>Affordability scale</td>
<td>Abacus price per month or course of therapy</td>
<td>Cost per year</td>
<td>Not specified, left to payers to evaluate</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 end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced disease: HR (death), OS, PFS, response rate</td>
<td>Vary, dependent on indication</td>
<td>Improvement in OS or surrogate end point</td>
<td>Vary, dependent on location</td>
<td>Advanced disease: OS, PFS, palliation of symptoms, response rate</td>
<td></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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td><strong>Secondary end points</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 factors</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 Adjuvant therapy: drug acquisition cost/entire treatment regimen</td>
<td>Total treatment cost</td>
<td>ASP/AWP</td>
<td>Total cost per person, total cost to payers</td>
<td>Not specified, left to payers to evaluate</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>

ASCO indicates American Society of Clinical Oncology; ASP, average sales price; AWP, average wholesale price; DFS, disease-free survival; ESMO, European Society for Medical Oncology; HR, hazard ratio; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; OS, overall survival; PFS, progression-free survival; R&D, research and development.

## 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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net health benefit</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Score (1-5) for each 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>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cost Readout</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Directly reported as regimen cost (WAC or ASP)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Advanced disease: drug acquisition cost per month</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Adjuvant therapy: drug acquisition cost for entire treatment</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Reported as relative affordability, considers overall cost of intervention (eg, cost of drug, infusions, supportive care, management)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<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>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cost per-year; cost-effectiveness of drug, with recommendations on what drug price should be to be cost-effective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Not specified; left to payers to evaluate</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Drug, cost, relative, or absolute value</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</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>

ASCO indicates American Society of Clinical Oncology; ASP, average sales price; ESMO, European Society for Medical Oncology; ICER, Institute for Clinical and Economic Review; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, National Comprehensive Cancer Network; WAC, wholesale acquisition cost.

These Value Frameworks Lend Insight to Payer-led Management Interventions

**Score for individual agents or regimens based on efficacy, safety, and cost**

---

**Formulary Positioning**

**Step Edits**

**Clinical Pathways**

---

Fundamental Differences Between I-O Therapies and Conventional Oncolytics Necessitate an Advanced Approach to Drug Evaluation

Conventional Oncolytics

Extended timeline, assessment at a greater number of time points

I-O Therapies

NK cell

T cell

Extended timeline, assessment at a greater number of time points
Magnitude and Duration Are Both Key Measures of Response for I-O Therapies
Immune Response with I-O Therapies Can Deepen and be Sustained Over Time

The immune response evolves and expands over time by constantly recognizing and remembering tumor antigens.

Some cytotoxic T cells mature into memory T cells and provide long-term immunity.

Cytotoxic T cells recognize and kill tumor cells.

Tumor cell death releases new antigens into the tumor microenvironment.

New antigens attract and activate new tumor antigen-specific T cells.

Cycle repeats.

As the immune response continues to expand, some cytotoxic T cells mature into memory T cells that may provide long-term immune protection, even if the original stimulus is no longer present.

Value Frameworks May Not Be Adequately Calibrated for the Assessment of I-O Agents

- Twenty-three metastatic indications for 6 I-O agents were approved by the FDA from March 2011 to August 2017
  - Ten (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
- Nine 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 I-O 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

Considerations on Pseudo-progression with I-O Therapies

While uncommon, pseudo-progression is an important consideration when evaluating response to I-O therapies.

<table>
<thead>
<tr>
<th>Disease progression</th>
<th>Pseudo-progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance status</strong></td>
<td>Deterioration of performance</td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td>Worsen</td>
</tr>
<tr>
<td><strong>Symptoms of tumor enlargement</strong></td>
<td>Present</td>
</tr>
<tr>
<td><strong>Tumor burden</strong></td>
<td>Increase</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>Increase</td>
</tr>
<tr>
<td><strong>New lesions</strong></td>
<td>Appear and increase in size</td>
</tr>
<tr>
<td><strong>Biopsy may reveal</strong></td>
<td>Evidence or tumor growth</td>
</tr>
</tbody>
</table>

I-O Therapies that modulate immune pathways may enable the immune system to attack healthy cells along with tumor cells: these events are known as imARs.

Throughout I-O treatment, HCPs should engage in the following:

- Educate and encourage patients and caregivers to monitor for and report symptoms of imARs.
- Remain vigilant throughout and after treatment to minimize complications, some of which may be life threatening.
- Use treatment algorithms to assist in managing immune-mediated Adverse Reactions.

As research in immune system activation advances and more data are made available, understanding and appropriate management of imARs will evolve.
Specialty Management Trends

- Utilization Management
  - Prior Authorization
  - Step Therapy
  - Quantity Limits
  - Site-of-Care Restrictions
  - ICER Evaluations

- Benefit Design
  - Specialty Formulary
  - Tier Status
  - Medical vs Pharmacy Benefit
  - Co-insurance/Deductibles
  - OOP Limitations

- Channel Management
  - Site of Care
  - Retail vs Specialty

- Coordination of Care
  - Disease Management
  - Specialty Care Management

- Contracting/Rebates
  - Preferred Products
  - Formulary Exclusions
  - Closed Formularies
  - Price Protection
Summary

• The specialty drug spend and trend for oncology has risen significantly and currently leads other classes in terms of growth

• Payer decision makers are increasingly tasked with managing these agents to provide quality health care that is economically sustainable

• Formulary decisions based on available evidence and value frameworks are crucial in managing the drug trend, but may require a revised approach for I-O agents

• A comprehensive evaluation of outcomes at various time points, incorporating both magnitude and duration of response is necessary for an accurate assessment of I-O agents

• A coordinated specialty management strategy is essential
Health Plan Strategies to Enhance Patient Outcomes with Immuno-Oncology Agents

John Fox, MD, MHA
Vice President, Associate Chief Medical Officer Medical Affairs
Priority Health
An Increasing Number of Targeted Oncology Agents are Being Developed

The Pipeline of Late Phase Oncology Molecules, 2007-2017

<table>
<thead>
<tr>
<th>Year</th>
<th>2007 (434)</th>
<th>2017 (710)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapies</td>
<td>0.9% (4)</td>
<td>0.4% (3)</td>
</tr>
<tr>
<td>Hormonals</td>
<td>3% (14)</td>
<td>2% (17)</td>
</tr>
<tr>
<td>Cytotoxics</td>
<td>15% (63)</td>
<td>8% (54)</td>
</tr>
<tr>
<td>Targeted Small Molecule</td>
<td>59% (254)</td>
<td>47% (335)</td>
</tr>
<tr>
<td>Targeted Biologics</td>
<td>23% (99)</td>
<td>42% (301)</td>
</tr>
</tbody>
</table>

Payers Have a Number of Levers for Managing Oncology Drug Therapies

Increasing Complexity

- Benefit Design
- Drug Dispensing
- Utilization Management
- Care Coordination
- Formulary placement
- Site-of-Care Management
- Contracting
- Disease Management
- Care Pathways
Utilization Management Strategies

- Formulary management including cross benefit management
- Prior authorization (PA)
- Step therapy (ST)
- Quantity limits (QL) for oral therapies
- Dose and vial size monitoring for infused drug
- Edits
Data Management and Support Can Streamline Patient Access and Drug Dispensation

The services should:

- Exchange information so that the prescriber (staff) only needs to enter it once
- Have a common “ID” so that the different transactions can be linked by multiple entities at different times
- Complete all actions required to get the patient on the right medication as soon as possible
- Integration of electronic medical records (EMRs) potentiates efficiency
Evolving Restrictions on Established Utilization Management Processes

- 17 states require all commercial health care plans to use an electronic prior authorization form in compliance with a national standard.
- Several states set time limits for prior authorization approvals.
- At least 18 states require exceptions to step therapy, specify time limits to respond to override requests or limit time step therapy can be mandated.
- Some states prohibit use of step therapy for patients who have gone through it previously with another health plan.

States Requiring Electronic Prior Authorization in Compliance with the NCPDP SCRIPT Standard

NCPDP=National Council for Prescription Drug Programs

Oncology PA: The Role of Companion and Complimentary 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

Complimentary 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 complimentary diagnostics that may be incorporated into PA criteria. These assays are based on PD-L1 titers predictive of response.

**Companion Diagnostics:**
- PD-L1 immunohistochemical (IHC) 22C3 pharmDx assay for pembrolizumab
- Ventana PD-L1 for atezolizumab

**Complimentary Diagnostics:**
- PD-L1 IHC 28-8 pharmDx for nivolumab
- Ventana PD-L1 for durvalumab

Role of lab developed tests vs. FDA approve tests

Balancing Benefit Design and Member Cost-Sharing Levers

- **Member cost-sharing**
  - High financial toxicity
  - High cost share reduces access to care for many patients
  - Adherence declines as cost rises, which may overall healthcare costs

- **Benefit design factors**
  - Medical vs pharmacy
  - Copay vs coinsurance/deductibles
    - Copay accumulator programs
  - Medicare Part B step therapy
  - Specialty tiers
  - In-network vs out-of-network

Concessions may depend on volume or share

Specialty Drug Contracting Approaches

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.

CMS OCM Program

• 5-year episode-of-care (EOC) program applicable to high-volume cancers (expected to cover 90% of cancer types)

• Medicare FFS program as part of a multi-payer model—applies to physician practices and PSA arrangements for provider-based services; but not to PPS exempt cancer hospitals

• Medicare pays $160 per beneficiary per month (PBPM) for a 6-month EOC ($960 per EOC), plus a retrospective performance-based payment
  • Payments in addition to Medicare FFS payment

• Performance-based payments (semi-annual)
  • Based on meeting applicable quality measures (preliminary set specified) – “performance multiplier” determines % of performance-based payment
  • Based on reducing cost at least 8% below a target threshold, with a 20% cap
  • Two-side risk allowed by no takers (yet)
• The most cost-effective oncology practices shared several key attributes ostensibly linked to an integrated care approach:
  • multicomponent health care system
  • conservative use of imaging
  • ongoing discussion of treatment options, risks, and benefits
  • early and standardized palliative care referrals
  • expanded access to ambulatory rapid response and same day management
  • optimized use of RNs for appropriate clinical interventions (proactive outreach, telephonic advice/triage for ED avoidance, hospital use avoidance)
Care Coordination Improves Outcomes

**NCI Study**

- Meta-analysis of 52 studies found care coordination improved 81% of outcomes, including screening, patient experience, quality end-of-life care.
- Most common care programs were:
  - Patient navigation
  - Home telehealth
  - Nurse case management

Care Coordination Reduces Confusion and Costs

Meridian Health Systems:
- Care coordinator communicates with patient, family, multiple specialists
- Reduces unnecessary imaging and testing
- Reduces hospitalizations from manageable complications such as dehydration.
- Earns patient satisfaction scores higher than 90%

• **Stanford**

  - Health coaches discuss goals for life with advanced cancer patients facing treatment failure or with less than three-year anticipated survival at diagnosis
    - Estimated reduction in costs, mostly from end-of-life care, of 14.5%
  - Health coach/nurse team assessed symptoms at intervention call center using decision-support systems.
    - Pre-stocked, individualized medication bundles were made available
    - Decreased ED visits, hospitalizations
    - Estimated cost reduction of 14%

Pathways Have Been Associated with Cost Savings in Oncology

The McKesson/US Oncology Experience in Colorectal Cancer Pathways

Summary

• Oncology treatment costs continue to rise sharply, driven by multi-therapy regimens and targeted therapies
• Utilization management more important than ever, but some traditional methods are now legislatively restricted and new ones may have unintended negative consequences
  • For I-O therapy specifically, companion and complimentary diagnostics may play a role in PA criteria according to predicted response
• In addition to streamlined PA methodology and site-of-care initiatives, disease management, care coordination, and clinical pathways offer innovative solutions in oncology management
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Option 1: Complete the online post-survey and evaluation form immediately following the live webcast. 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 webcast, please note that a personalized evaluation link will be emailed to you following the webcast 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: **immuno19**

You will then need to log in or create an account ensuring your NABP information is entered and correct. Be sure to enter today’s date, **April 18, 2019**, 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.**
THE IMMUNO-ONCOLOGY TRANSFORMATION:
Implications for Managed Care

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