THE IMMUNO-ONCOLOGY TRANSFORMATION: Implications for Managed Care

This activity is supported by independent educational grants from Bristol-Myers Squibb and Merck & Co., Inc.
Assessing the Clinical Benefits and Appropriate Use of Immuno-Oncology Agents

Joan H. Schiller, MD
Professor
University of Virginia
Evidence Pointing Toward Immune Reactivity to Tumors

• Tumors that have severe lympho- reticular infiltration have a better prognosis than those that do not.
• Certain tumors regress “spontaneously.”
• Increased incidence of primary and secondary malignancies (particularly lympho- reticular tumors) in immunodeficient patients.
• Antibodies and immune T lymphocytes have been detected in patients with tumors.
• The young and the very old have an increased occurrence of tumors.
• Animals can be specifically immunized against various types of tumors.
Tumors express a multitude of proteins, known as tumor-associated antigens. Tumor-associated antigens can trigger a tumor-specific immune cell response:


T-cell activation: cytotoxic T cells

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

Inactive T cell

Activated T cell

Activated APC

Antigen

Co-stimulatory signal

Activated T cell

T cells proliferate

Activated, cytotoxic (killer) T cells

Antigen recognition

Tumor cell

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

5. **Cytotoxic T cell**
How Does T-Cell Activation Happen?

Activated T Cells $\rightarrow$ Recognize Tumor Associated Antigens on Tumor Cells

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

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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  

**Lymph Nodes**

**Tumor**

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**

Primining phase

Cytokines

--- Inhibitory Signal

**Tumor**

--- Inhibitory Signal

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

---

CTLA4 Antibodies: Inhibit the “Priming” Phase

• Antigen presentation and ligation of B7/CD28 co-activators results in T-cell activation: A GOOD thing for combating cancer, but a BAD thing which can result in autoimmune diseases if not stopped

• In the activated T cell, CTLA-4 competes with CD28 and acts as the brakes on T-cell activation by binding to B7

• By inhibiting CTLA-4, ipilimumab releases the natural braking system and restores T-cell activation, allowing T-cell proliferation to continue

PD-1 and PD-L1 Antibodies: Inhibit the Effector Phase

- PD-1 is an inhibitory receptor found on activated lymphocytes and monocytes
- Binds with PD-L1 on tumor cells
- Interaction between PD-1 and PD-L1 suppresses the cytotoxic T cell response: A BAD thing for combating cancer, but a GOOD thing for preventing autoimmune diseases
- Inhibition of PD-1 associated with tumor immune escape

### 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></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></td>
</tr>
<tr>
<td>Avelumab</td>
<td>Anti–PD-L1</td>
</tr>
<tr>
<td>Durvalumab</td>
<td></td>
</tr>
</tbody>
</table>

Ipilimumab OS at 3 years and Beyond in Phase 2 and 3 Trials of Melanoma

Median OS: 11.4 mo (95% CI: 10.7-12.1)
3-yr OS rate: 22% (95% CI: 20% to 24%)

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>
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<table>
<thead>
<tr>
<th>Time, mo</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>24</th>
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<tbody>
<tr>
<td>No. at Risk</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Nivolumab</td>
<td>453</td>
<td>399</td>
<td>353</td>
<td>332</td>
<td>311</td>
<td>291</td>
<td>249</td>
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<tr>
<td>Ipilimumab</td>
<td>453</td>
<td>364</td>
<td>314</td>
<td>209</td>
<td>252</td>
<td>225</td>
<td>184</td>
<td>56</td>
</tr>
</tbody>
</table>

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

A. PFS in the ITT Population¹

<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 Population²

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (96% CI), mo</td>
<td>NR (34.7 NR)</td>
<td>26.7 (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 (96% CI), %</td>
<td>66.2 (61.7-70.4)</td>
<td>55.6 (46.9-61.8)</td>
</tr>
</tbody>
</table>

Stratified HR for death (99.73% CI)

Durvalumab: 0.53 (0.47-0.997)

Two-sided P: .0025

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%

Overall Survival (%)

Time (months)

No. of Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Atezolizumab</th>
<th>Docetaxel</th>
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<tbody>
<tr>
<td>24</td>
<td>425</td>
<td>425</td>
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<td>119</td>
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<td>2</td>
<td>98</td>
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Overall Survival, ITT

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td>3</td>
<td>410</td>
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<tr>
<td>6</td>
<td>377</td>
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<td>9</td>
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<td>12</td>
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<td>18</td>
<td>71</td>
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<tr>
<td>21</td>
<td>18</td>
</tr>
</tbody>
</table>

OS, %

- Pembro/Pem/Plat: 69.2% (49.4%)
- Placebo/Pem/Plat: 52.4% (49.4%)

Median (96% CI)

- NR (NE-NE)
- 11.3 mo (8.7-15.1)

Events HR (95% CI) P

- Pembro/Pem/Plat: 31.0% 0.49 <0.00001
- Placebo/Pem/Plat: 52.4% (0.38-0.64)

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.
**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

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

**Platinum-Doublet Chemotherapy (4-6 cycles)**
- Carbo + pemetrexed*
- Cis + pemetrexed*
- Carbo + gemcitabine
- Cis + gemcitabine
- Carbo + paclitaxel

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

R (1:1)
N = 305

*Reck, et al; NEJM 2016*
Pembrolizumab vs Chemo in 1st Line NSCLC


### Overall Survival

<table>
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<tr>
<th>Time, months</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
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<tbody>
<tr>
<td>OS, %</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
<td>50</td>
<td>40</td>
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</table>

- **Pembro**: 80% at 3 months, 72% at 6 months, 70% at 9 months
- **Chemo**: 80% at 3 months, 72% at 6 months, 54% at 9 months

### Events, Median, HR (95% CI), P

<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>Pembro</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>
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</table>

No. at risk:

<table>
<thead>
<tr>
<th></th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>154</td>
<td>136</td>
<td>121</td>
<td>82</td>
<td>39</td>
<td>11</td>
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<tr>
<td>Chemo</td>
<td>151</td>
<td>123</td>
<td>106</td>
<td>64</td>
<td>34</td>
<td>7</td>
<td>1</td>
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</tbody>
</table>

Data cut-off: May 9, 2016
CheckMate 227: Nivo + Ipi in 1L NSCLC With High TMB (≥10 mut/Mb)

CheckMate 227 Part 1 Study Design

Key Eligibility Criteria
- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No known sensitizing EGFR/ALK alterations
- ECOG PS 0–1

Stratified by SQ vs NSQ

Co-primary endpoints: Nivolumab + ipilimumab vs chemotherapy
- OS in PD-L1-selected populations
- PFS in TMB-selected populations

Database lock: January 24, 2018; minimum follow-up: 11.2 months
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>
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</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


aORR for all treated patients: 41% in PD-L1 ≥1% subgroup (n=138) and 15% in PD-L1 <1% subgroup 114; bCR=0; cCR=16%; dCR=4%; eCR=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 ofMismatch 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

Compliment System

Lag-3

Single Cell Characterization of the Immunological Microenvironment
Predicting response to Checkpoint inhibitors
Tumor microenvironment (cont.)

MA11 - Biomarkers of IO Response (ID 912)
Type: Mini Oral Abstract Session  |  Track: Immunooncology  |  Presentations: 12

Moderators: Govind Babu Kanakasetty, Shirish Gadgeel
Coordinates: 9/25/2018, 10:30 - 12:00, Room 203 BD

T Cell Intrinsic vs Extrinsic PD-1 Blockade

MA11.01 - Comparative Efficacy of T-Cell Intrinsic Versus Extrinsic PD-1 Blockade to Overcome PD-L1+ Tumor-Mediated Exhaustion (Now Available)
10:30 - 10:35  |  Presenting Author(s): Jordan Dozier  |  Author(s): Nan Chen, Jasmeen Saini, Navin Chintala, Prasad S. Adusumilli

CD3+ TIL Infiltration and FOXP3+/CD8+ Ratio

MA11.02 - Increased CD3+ TIL Infiltration and Low FOXP3+/CD8+ TIL Ratio Can Predict Anti-PD-1 Therapeutic Response in Non-Small Cell Lung Cancer Patients (Now Available)
10:35 - 10:40  |  Presenting Author(s): Hyojin Kim  |  Author(s): Hyun Jung Kwon, Yeon Bi Han, Soo Young Park, Eun Sun Kim, Jin-Haeng Chung

TIL Infiltration and Cancer Nuclei

MA11.03 - Interaction of Tumor Infiltrating Lymphocytes and Cancer Nuclei Predicts Response to Nivolumab in Non-Small Cell Lung Cancer (NSCLC) (Now Available)
10:40 - 10:45  |  Presenting Author(s): Xiangxue Wang  |  Author(s): Cristian Barrera, Cheng Lu, Vamsidhar Velcheti, Anant Madabushni
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

*Grade 3/4 Uncommon*
- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Colitis
- Dermatitis
  - Macropapular/pruritus
- Pneumonitis
- Hepatitis
- Pancreatitits
- 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%

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
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<tbody>
<tr>
<td>Grade 1</td>
<td>• Supportive care +/- hold drug</td>
</tr>
<tr>
<td>Grade 2</td>
<td>• Hold drug</td>
</tr>
<tr>
<td></td>
<td>• Re-dose at lower dose once toxicity resolved to $\leq$ Grade 1</td>
</tr>
<tr>
<td></td>
<td>• Low dose steroids if symptoms do not resolve in 1 week</td>
</tr>
<tr>
<td>Grade 3/4</td>
<td>• D/C drug</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>• High dose steroids</td>
</tr>
<tr>
<td></td>
<td>• Taper over $\geq$ 1 month until toxicity resolves to $\leq$ Grade 1</td>
</tr>
</tbody>
</table>
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)

0% 10% 20% 30% 40% 50% 60% 70% 80% 90%

Toxicity of CAR-T Cells

- 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

Summary

• 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>TREND</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inflammatory conditions</td>
<td>$160</td>
<td>14.1%</td>
</tr>
<tr>
<td>2. Diabetes</td>
<td>$80</td>
<td>4.1%</td>
</tr>
<tr>
<td>3. Oncology</td>
<td>$120</td>
<td>18.1%</td>
</tr>
<tr>
<td>4. Multiple Sclerosis</td>
<td>$120</td>
<td>-4.8%</td>
</tr>
<tr>
<td>5. HIV</td>
<td>$70</td>
<td>11.7%</td>
</tr>
<tr>
<td>6. Pain/Inflammation</td>
<td>$60</td>
<td>-11.1%</td>
</tr>
<tr>
<td>7. Attention disorders</td>
<td>$50</td>
<td>-8.2%</td>
</tr>
<tr>
<td>8. Asthma</td>
<td>$40</td>
<td>-7.3%</td>
</tr>
<tr>
<td>9. High blood pressure/heart disease</td>
<td>$40</td>
<td>-13.4%</td>
</tr>
<tr>
<td>10. Depression</td>
<td>$30</td>
<td>-3.8%</td>
</tr>
<tr>
<td>11. Skin conditions</td>
<td>$30</td>
<td>4.8%</td>
</tr>
<tr>
<td>12. Contraceptives</td>
<td>$20</td>
<td>-9.6%</td>
</tr>
<tr>
<td>13. High blood cholesterol</td>
<td>$20</td>
<td>-27.0%</td>
</tr>
<tr>
<td>14. Anticoagulants</td>
<td>$10</td>
<td>11.7%</td>
</tr>
<tr>
<td>15. Seizures</td>
<td>$10</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

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>Description</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...

Covered differently

- 36%
- 64%

the majority were covered the same way...

Covered the same way by all or most (>75%) plans

and specifically the decisions were...

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

• 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

## Formulary Exclusion Classes

<table>
<thead>
<tr>
<th>Condition</th>
<th>2016 (n=158)</th>
<th>2017 (n=152)</th>
<th>Significantly higher than comparison year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis C</td>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory conditions</td>
<td>47%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Fertility</td>
<td>48%</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>46%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Growth deficiency</td>
<td>26%</td>
<td>32%</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>36%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Infused/ injectable oncology</td>
<td>25%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Lung/ breathing disorders</td>
<td>24%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Oral oncology</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>22%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>19%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Hemophilia/ bleeding disorders</td>
<td>19%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>20%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>9%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

**Base:** Respondents who have formulary exclusions in place. Multiple responses allowed. NA = not asked. 
N=299 employer-based plans of all sizes

Classes Under Consideration for Formulary Exclusion

45% 38% 38% 37% 39% 38% 38% 38% 37% 34% 29% 28% 25% 25% 25% 25% 22% 21% 12% 11% 12%

Hepatitis C Multiple sclerosis Cholesterol Inflammatory conditions Lung/breathing disorders Infused/injectable oncology Growth deficiency Hemophilia/bleeding disorders HIV Oral oncology Cystic fibrosis Fertility Other

2016 (n=110) 2017 (n=102)

Base: Respondents who are considering formulary exclusions. Multiple responses allowed. NA = not asked.

N=299 employer-based plans of all sizes

Potential Factors in Oncology Formulary Decision Making

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
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)
Clinical Evidence & Cost-Effectiveness

- 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>Value Framework&lt;sup&gt;6-10&lt;/sup&gt;</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>Patient</td>
<td>Physician</td>
<td>Payer</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>Value Framework&lt;sup&gt;6-10&lt;/sup&gt;</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>Yes</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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 specified, left to payers to evaluate</td>
<td></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>

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.

<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><strong>Cost Readout</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug, cost, relative, or absolute value</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cost to patient</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cost to healthcare system</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>

**Value Frameworks 6-10**

<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><strong>Cost Readout</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug, cost, relative, or absolute value</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cost to patient</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cost to healthcare system</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

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

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

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.

Key Oncology Outcomes Must Be Weighed and Evaluated Differently for I-O Therapies

• Overall Survival (OS)
  • The time from randomization until death from any cause
  • Gold standard in oncology outcomes where the aim is to prolong life

• Progression Free Survival (PFS)
  • The time from randomization until disease progression or death from any cause
  • Less influenced by subsequent therapy than OS and more relevant with targeted agents than response

• Objective Response Rate (ORR)
  • Direct or indirect measure of tumor burden
  • Measures a specific response to a therapeutic intervention rather than survival
A Comprehensive Approach to Assessing Outcomes for I-O Therapies

**OS/PFS**
- **HR/RR reduction**: Measures the magnitude of difference between two curves of a Kaplan-Meier Plot.
- **Assess potential benefit across the duration of the trial**.
- **Assess potential benefit at specific time points of interest**.

**Median Duration**
- The time point at which 50% of patients have either progressed or died.

**Time Point Analyses**
- Estimate the presence or absence of sustained benefit at time points of interest (e.g., 12 months).

OS = Overall survival
PFS = Progression-free survival
HR = Hazard ratio
RR = Relative risk
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></th>
<th>Disease progression</th>
<th>Pseudo-progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance status</strong></td>
<td>Deterioration of performance</td>
<td>Remains stable or improves</td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td>Worsen</td>
<td>May or may not improve</td>
</tr>
<tr>
<td><strong>Symptoms of tumor enlargement</strong></td>
<td>Present</td>
<td>May or may not be present</td>
</tr>
<tr>
<td><strong>Tumor burden</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Increase</td>
<td>Initial increase followed by response</td>
</tr>
<tr>
<td>New lesions</td>
<td>Appear and increase in size</td>
<td>Appear then remain stable and/or subsequently respond</td>
</tr>
<tr>
<td>Biopsy may reveal</td>
<td>Evidence or tumor growth</td>
<td>Evidence of immune-cell infiltration</td>
</tr>
</tbody>
</table>

Safety Considerations: Immune-mediated Adverse Reactions (imARs)

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

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

*Increasing Complexity*
Utilization Management Strategies

• Prior authorization (PA)
  • Requires plan review for appropriate drug utilization and subsequent authorization
  • Frequently based on FDA-approved indication and labelling
  • Assessment of biomarker status

• Step therapy (ST)
  • The claims system “looks” for required drugs to use prior to coverage of requested agents, usually pharmacy benefit

• Quantity limits (QL)
  • Allows a limit to be placed on medications to ensure proper usage of dosage forms, allowing maximum daily dosages
  • Dose optimization
  • Vial size management
  • Partial fill for oral and self-administered therapies

• Edits
  • Age
  • Drug-Drug interactions
  • For the management of dosing/frequency
  • Retrospective DUR

• Care management
  • Pharmacy involvement/coordination, in-house vs. carve-out
  • Side effect and toxicity management
**PA Remains the Most Prevalent Tool for Utilization Management Among Payers**

| Use of Selected Utilization/Clinical Management Tools, Percentage of Plans | 2017 |
|---|---|---|
| Smaller Plans (≤ 400,000 Lives) | Medium/Large Plans (>400,000 Lives) | All Plans |
| Site-of-care program | 44% | 95% | 61% |
| Partial fill program | 56% | 60% | 58% |
| Prior authorization* | 92% | 95% | 93% |
| Electronic prior authorization | 21% | 45% | 29% |


*Used a PA program for specialty drugs in the medical benefit.

ePA=electronic prior authorization; PA=prior authorization.
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.

Statewide Formularies Are Being Proposed to Drive Coverage Consistency and Uniform Access

- Specifically for providers who receive state funds
- Coordinate with a wide array of stakeholders:
  - The state Medicaid authority
  - Health and Human Services organizations
  - State hospitals
  - Department of Corrections/County Sheriff’s Office (jails/prisons)
- Current bills related to statewide formularies do not:
  - Mandate what a prescriber can and can’t prescribe
  - Directly affect the informed consent/medication decision process, which is highly individualized
  - Preclude a facility from having a non-formulary request or med pre-authorization system in place

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
Sample PA Criteria for Immuno-therapy in Metastatic NSCLC

**Pembrolizumab**

PA Requirements Related to NSCLC:

1. Following disease progression on or after platinum-containing chemotherapy, and EGFR- or ALK-targeted therapies for EGFR- or ALK-mutated disease, in a patient whose tumor expresses PD-L1 [Tumor Proportion Score (TPS) \( \geq \)1\%] as determined by an FDA-approved test.

2. *First-line treatment* (no prior chemotherapy treatment for metastatic NSCLC) in a patient whose tumor has high PD-L1 expression (TPS \( \geq \)50\%) as determined by an FDA-approved test, with no EGFR- or ALK-mutated disease.

3. *First-line treatment* in a patient with non-squamous NSCLC in combination with pemetrexed and carboplatin, with no EGFR- or ALK-mutated disease.

4. *First-line treatment* in patient with squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel.

**Nivolumab**

PA Requirements Related to NSCLC:

Following disease progression with previous

a) platinum-based chemotherapy or

b) EGFR or ALK targeted Txs for EGFR/ALK mutated Dz.

**Atezolizumab**

PA Requirements Related to NSCLC:

- Experienced disease progression during or following platinum-containing chemotherapy.
- Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
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

<table>
<thead>
<tr>
<th>Place of Service</th>
<th>Cost per Unit</th>
<th>Units</th>
<th>Cost Per Claim</th>
<th>Claims per Year</th>
<th>Annual Cost</th>
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<tr>
<td>MD office</td>
<td>$30</td>
<td>215</td>
<td>$6,450</td>
<td>7</td>
<td>$45,150</td>
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<tr>
<td>HOPD (average)</td>
<td>$48</td>
<td>215</td>
<td>$10,320</td>
<td>7</td>
<td>$72,240</td>
</tr>
<tr>
<td>HOPD (highest cost hospital)</td>
<td>$150</td>
<td>215</td>
<td>$32,250</td>
<td>7</td>
<td>$225,750</td>
</tr>
</tbody>
</table>

HOPD=hospital outpatient department.
Internal Utilization and Pricing Data.

*Dispensation or administration outside of the hospital/facility setting is favorable when possible in terms of cost management and is central to site of care optimization efforts*

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.

**Traditional Contracting**
- Flat, Volume or Share-Based
  - Rebate %s for Purchased Brand A
  - Concessions may depend on volume or share

**Value-Based Contracting**
- Indication-Based
  - Rebate specific to an indication
- Regimen-Based
  - Rebate paid when two products used in combination
- “Outcomes-” Based
  - Concessions depend on how “well” the drug works for a patient/cohort


Drug manufacturers will increasingly find themselves involved in such arrangements with payers when applicable.

**Increasing Data & Complexity**
Contracting with High-Quality, Cost-Efficient Providers: Oncology Practices

Among oncology practices positively deviant in terms of charges to payers, the more cost-effective 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)

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)
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%
Clinical Pathways Initiatives Aim to Reduce Treatment Variability While Allowing Individualized Care in Oncology

Balancing treatment *standardization with personalization* is cited among the top three challenges in cancer care for more than a third of MCOs.

**Goal of Clinical Pathways Initiatives**

- Guideline-based Care
- Personalized Medicine

Pathways Have Been Associated with Cost Savings in Oncology

The McKesson/US Oncology Experience in Colorectal Cancer Pathways

Providers Support Guidelines and Pathways

• Oncologists are rapidly adopting guidelines and pathways, too:
  • Practices report compliance with pathways increased 42% from 2014-2016 and twice as fast 2016-2017
  • 78% of oncologists used guidelines in 2017, up from 53% in 2016

• Increasingly, practicing oncologists play a central role in pathway development

• When efficacy and safety are comparable

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
THE IMMUNO-ONCOLOGY TRANSFORMATION:
Implications for Managed Care

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