Immunotherapy and Cancer: The Progress Continues

Rowena (Moe) Schwartz, PharmD, BCOP
University of Cincinnati

Recent Progress in Immunotherapy in Cancer Care

- Approval of new medications and strategies for cancer treatment continue to increase the number of treatment options for individuals with cancer.

- Optimizing the clinical applications of medications with results of clinical trials:
  - Determining patient and/or population selection
  - Clarifying the place in therapy
  - Strategies to mitigation and management of toxicities

- Integration of drug therapy into cancer care
“Hand clapping for science is now inextricably linked to hand wringing over affordability.”

Bach PB. New Math on Cost Effectiveness. NEJM 373:19:1798

The Immune System

Immunity:
- The body’s ability to resist disease
- Ability of the body to respond to foreign substances (microbes and noninfectious molecules)

Immune system:
- Network (cells, proteins, tissues, organs and molecules) that works together to defend the body against attacks by foreign invaders.

Immune response:
- Coordinated reaction of cells and molecules of the immune system
In the beginning….

William Bradley Coley, MD (1862 – 1936)

Evolution of Cancer Immunotherapy

- Nonspecific immunostimulants (unknown mechanisms of action)
- Recombinant cytokines (IL-2, IFN)
- Humanized and human monoclonal antibodies (mAbs) to cell surface receptor proteins
- Vaccinations strategies
- Immune checkpoint inhibitors (mAbs)
- Cellular therapies: TILs, CAR T cells
  TILs = tumor infiltrating lymphocytes
  CAR T cells = chimeric antigen receptor T cells

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Cytokines

- A large family of low molecular weight soluble proteins involved in the regulating cellular activity and mediates the immune and inflammatory reactions
- Act as messengers within the immune system and between the immune system and other systems of the body
- Some cytokines have direct role in immune defense (e.g. interferon are released by virally infected cells to establish viral resistance)
- Cytokines are produced by many immune cells including mast cells, dendritic cells, macrophages

<table>
<thead>
<tr>
<th>Example of Cytokines</th>
<th>Principal Cellular Source(s)</th>
<th>Biologic Effects</th>
</tr>
</thead>
</table>
| Interleukin 1 (IL-1) | Macrophages, DC, keratinocytes | Endothelial cells: activation (inflammation, vasodilation) 
Hypothalamus: fever |
| Interleukin 2 (IL-2) | T cells | T cell proliferation and differentiation into effector and memory cells; stimulation regulatory T cell development, conversion and function; NK cell proliferation and activation |
| Interferon-α (IFN-α) | NK and T cells | Increased expression of MHC class I; NK cell activation |
| Tumor necrosis factor (TNF) | Macrophages, NK cells | Increased class I MHC expression; NK cell activation |
| Interleukin-1α (IL-1α) | Macrophages, DC, endothelial cells, keratinocytes | Endothelial cells: activation (inflammation, vasodilation) 
Hypothalamus: fever 
Liver: synthesis of acute-phase proteins |

Early Strategies for Immunotherapy: Interleukin 2

Aldesleukin (Proleukin®)

Response to interleukin-2 in melanoma:
- Overall responses were about 16% (CR 6%) - responses seen in all disease sites - responses seen in pts with large disease burden
- median duration response 8.9 months (range: 1.5 - 122 + months)
- patients responding more than 30 months → stable disease
- patient who had not received other treatments where the most likely to response

Aldesleukin (rIL2): Toxicity

Capillary leak syndrome
**Aldesleukin (Proleukin®)**

Indications per package insert in 2018:
- metastatic renal cell cancer
- metastatic melanoma

“Careful patient selection is mandatory.”
Evaluation of PS, cardiac, renal, liver and pulmonary function is required.

**Evolution of Cancer Immunotherapy**

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**Antibody**
Cell Surface Antigens on B Cell

Target: CD20
- Transmembrane protein located on pre-B and mature B lymphocytes.
- Not found on stem cells, pro-B cells.

Rituximab (Rituxan®)
Targeting CD20 on B cells

**Strategies:**
- Rituximab (Rituxan)
- Obinutuzumab (Gazyva)
- Ofatumumab (Arzerra)
- Radioimmunotherapy: ibritumomab tiuxetan (Zevalin)
- Rituximab + hyaluronidase (Rituxan Hycela)

**Applications in cancer:**
- NHL (follicular, DLBCL, mantle cell, waldenstrom)
- Chronic lymphocytic leukemia

**Warning:**
- Hepatitis B virus reactivation
- Progressive multifocal leukoencephalopathy

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**Rituximab and Hyaluronidase (Rituxan Hycela®)**

**Administration:** subcutaneous use only

**Indications:**
- Follicular lymphoma
  - Relapsed or refractory FL
  - Previously untreated FL in combination with chemotherapy
  - Patients achieving CR or PR to rituximab + chemotherapy as single agent maintenance
  - Non-progressing FL as single agent after first line chemotherapy (CVP)
- Diffuse large B-cell lymphoma
  - Previously untreated DLBCL + chemotherapy
- CLL

All patients must receive at least one full dose of rituximab product by intravenous infusion before receiving Rituxan Hycela by SQ infusion.

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**Monoclonal Antibodies: Optimizing the approach**
Cell Surface Antigens on B Cell

Target: CD22

The Target:
- Cell-surface glycoprotein expressed in > 90% patients with B-cell ALL
  - Not shed into the extracellular matrix

The Strategy:
- Humanized anti-CD22 monoclonal antibody **conjugated** to calicheamicin
- Conjugate binds to CD22 on B cell, internalized and the calicheamicin is released → DNA strand breaks and apoptosis

Inotuzumab Ozogamicin (Besponsa™)
Inotuzumab Ozagamicin (Besponsa™)
Phase III trial in adults with relapsed or refractory ALL randomized to receive inotuzumab ozagamicin vs standard chemotherapy (n=326)

- Methods:
  - Inotuzumab ozagamicin:
    - 1.8 mg/m² IV per cycle (0.8 mg/m² on day 1, 0.5 mg/m² on day 8 and 15) q 21 (first cycle) then q 28 days (six cycles).
    - If a patient achieved CR the dose on day 1 of each cycle was reduced to 0.5 mg/m².
  - Standard chemotherapy of investigator choice including FLAG, fludarabine + GCSF or cytarabine + mitoxantrone

- Results:
  - CR: 80.7% (IO) vs 29.4% (chemo)
  - Duration of remission: 4.6 mo (IO) vs 3.1 mo (chemo)
  - OS: 7.7 mo (IO) vs 6.7 mo (chemo)
  - Toxicity: ↑ liver disease in inotuzumab ozagamicin group


Inotuzumab Ozagamicin Indications:
- Treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.
- Premedication with corticosteroids, antipyretic and antihistamine prior to all infusion per package insert.

Clinical trials ongoing in CD22+ aggressive B-NHL.
**Epidermal Growth Factor Family of Cell Surface Receptors (ErbB)**

- **Extracellular Domain**
- **Transmembrane Domain**
- **Intracellular TK Domain**

**ErbB1/EGFr**
**ErbB2/HER2/neu**
**ErbB3/HER3**
**ErbB4/HER4**

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**Epidermal Growth Factor Receptor Family**

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**HER2/neu as a Drug Target**

- HER-2 is a transmembrane receptor tyrosine kinase (epidermal growth factor receptor tyrosine kinase family)
- Amplified/over expression in 20-30% women with breast cancer
- More common in premenopausal women
- Used to determine patients who may benefit from therapy directed at HER2/neu

- Trastuzumab (Herceptin®)
- ado-trastuzumab emtansine (Kadcyla®)
- Pertuzumab (Perjeta®)
- Lapatinib (Tykerb®)
- Neratinib (Nerlynx®)
Targeting VEGF and VEGF Receptor

Target: CD38

- Transmembrane glycoprotein expressed on the surface of hematopoietic cells (including myeloma cells)
- Functions:
  - Receptor mediated adhesion
  - Signaling
  - Modulation of protein activity

Daratumumab (Darzalex®)
Daratumumab: FDA Approval

At launch in 2015:
• Daratumumab is approved as a single agent for the treatment of patients with myeloma who have received >3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double-refractory to both a PI and IMiD.

After drug became available additional indications included:
• In combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone for treatment of patients with myeloma who have received at least one prior therapy.
• In combination with pomalidomide and dexamethasone for the treatment of patients with myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

Target: Platelet-Derived Growth Factor

• Platelet-derived growth factor (PDGF) + PDGF receptor
  → signaling in mesenchymal biology
  → aberrant cellular signaling
  → modulating tumor or stromal microenvironment
• Olaratumab binds PDGF receptors blocking PDGF-AA, PDGF-BB and PDGF-CC binding and receptor activation
• True mechanism of action for tumor activity?

Olaratumab Target: Platelet-Derived Growth Factor

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Talimogene laherparepvec (IMLYGIC®)

- Talimogene laherparepvec is a genetically modified oncolytic viral therapy.
  - engineered, oncolytic herpes simplex virus type-1 (HSV-1)
  - oncolytic viruses selectively recognize, infect and destroy malignant cells with minimal effects on normal cells.
Talimogene laherparepvec

• Indication:
  • Local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.
  • Limitations per package insert: This therapy has not been shown to improve OS or have an effect on visceral metastases

Talimogene laherparepvec (TVEC)

• Contraindications:
  • Immunocompromised patients
  • Pregnant patients

• Warnings and Precautions:
  • Accidental exposure → may lead to transmission of herpetic infection
  • Herpetic infections
  • Injection site complications
  • Immune-mediated event
  • Plasmacytoma at injection site

Immunity and Cancer
The Cancer-Immunity Cycle

T Cell Activation
- Mapped out the molecular mechanism of T cell recognition, regulation and function
- Blocking negative immune regulators (checkpoints) may give the human immune system the power to fight cancer

T-cell Regulation
Target: Immune Checkpoint

Activation of T cells to enhance antitumor response:
• Antigen-specific signal mediated by the T-cell receptor (TCR)
• Co-stimulatory signal mediated by stimulatory and inhibitory receptor and ligand pairs (immune checkpoints)

Immune Checkpoint Blockade

• Activation of T cells to enhance antitumor response:
  • Antigen-specific signal mediated by the T-cell receptor (TCR)
  • Co-stimulatory signal mediated by stimulatory and inhibitory receptor and ligand pairs (immune checkpoints)

Checkpoints:
• Cytotoxic T lymphocyte antigen-4 (CTLA-4)/Operational during early activation of T cells
• PD-1/PD-L1 (PD-programmed death)/Operational during the effector phase of T-cell activation

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**T-cell Activation**

[Diagram of T-cell activation]

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**Ipilimumab: Phase III**

Patients (n=502) with previously untreated metastatic melanoma randomized:
- ipilimumab + dacarbazine
- dacarbazine + placebo

<table>
<thead>
<tr>
<th>Survival</th>
<th>Ipi + dacarbazine</th>
<th>Dacarbazine + placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>11.2</td>
<td>9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 yr OS (%)</td>
<td>47.2</td>
<td>36.3</td>
<td>NA</td>
</tr>
<tr>
<td>2 yr OS (%)</td>
<td>28.5</td>
<td>17.9</td>
<td>NA</td>
</tr>
<tr>
<td>3 yr OS (%)</td>
<td>20.8</td>
<td>12.2</td>
<td>NA</td>
</tr>
</tbody>
</table>


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**Ipilimumab (Yervoy®)**

- **Durability** of responses were seen in phase III trials.
- Retrospective evaluation of individuals (n = 377) treated on early clinical trials:
  - Patients that achieved CR may have long-lasting response
  - Patients who had a PR may achieve long-term disease control
  - Response to ipilimumab can be delayed


- **Immune-related response criteria (irRC)**:
  - New lesions are included in the determination of overall tumor burden but do not automatically indicate progressive disease
  - Evidence of disease progression requires confirmation with radiographic assessment at least 4 weeks later

Ipilimumab (Yervoy®)

Melanoma:
- Treatment of unresectable melanoma
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy. (Oct 28, 2015)

Immune Related Response Criteria (IRRC)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Change in Baseline in Total Tumor Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>irCR</td>
<td>Decrease by 100% (complete resolution)</td>
</tr>
<tr>
<td>irPR</td>
<td>Decrease by ≥ 50%</td>
</tr>
<tr>
<td>irPD</td>
<td>Increase by ≥ 25%</td>
</tr>
<tr>
<td>irSD</td>
<td>Any response not inclusive of above criteria</td>
</tr>
</tbody>
</table>


Ipilimumab: Adverse Events

- The potent ability of CTLA-4 blockade activates the immune system resulting in a variety of clinical effects.
- Tissue specific inflammation
  - Skin → dermatitis
  - Gastrointestinal tract → enterocolitis
  - Liver → hepatitis
  - Endocrine system → hypophysitis, thyroditis
- Immune-related adverse events (irAE)
  - Usually transient and reversible
  - Patient education for early recognition
  - Interventions depend on severity and side effect
  - Interrupt dose
  - Immunosuppression (e.g. steroids)

T-cell Regulation


PD-1 Receptor

Programmed death-1 (PD-1) is a transmembrane receptor member:
• Is upregulated on activated T-cells
• Engages two ligands → PD-L1 and PD-L2

PD-L1 (B7-H1)
• Expression is upregulated by cytokines (e.g. gamma interferon)
• Can suppress immunity by binding to CD80

PD-L2 (B7-DC)
• Has a higher binding affinity than PD-L1 for PD-1
• Expressed on dendritic cells, macrophages and some tumors


PD-1 / PD-L1 Inhibitors

• PD-1 Inhibitor
  • Pembrolizumab (Keytruda®)
  • Nivolumab (Opdivo®)

• PD-L1 Inhibitor
  • Atezolizumab (Tecentriq®)
  • Avelumab (Bavencio®)
  • Durvalumab (Imfinzi®)
Pembrolizumab (Keytruda)

Disease included in current indications per package insert:

- Melanoma
- Non-small cell lung cancer
- Head and neck cancer (squamous cell)
- Urothelial cancer
- Gastric cancer
- Classical Hodgkin disease
- Microsatellite instability –high cancer

Initially approved as 2 mg/kg IV q 2 weeks → 200 mg IV q 3 weeks for adults

Nivolumab (Opdivo)

Disease included in current indications per package insert:

- Melanoma (new indication for adjuvant therapy)
- Non-small cell lung cancer **
- Head and neck cancer (squamous cell)
- Urothelial cancer **
- Hepatocellular carcinoma **
- Microsatellite instability –high cancer or mismatched repair deficient metastatic colon cancer**
- Renal cell cancer **
- Classical Hodgkin Disease

- Initial dosing when approved was 3 mg/kg IV q 2 weeks
- Flat dose of 240 mg IV q 2 weeks was approved for some indication (**)

Nivolumab in Melanoma (CheckMate-066)

Focus on T-cell Activation


Atezolizumab (Tecentriq)

Disease included in current Indications per package insert:
• Urothelial cancer
• Non-small cell lung cancer

Dose per package insert is flat dose of 1200 mg IV q 2 weeks

Atezolizumab

Indications:
• Treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy or who have disease progression during or following platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy
• Treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with ALK or EGFR genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Atezolizumab.
Avelumab (Bavencio)

Disease included in current Indications per package insert:
• Merkel cell carcinoma
• Urothelial cancer

- Premedication for first 4 doses, and subsequent dose as needed
- Dose per package insert is 10 mg/kg IV over 60 minutes q 2 weeks

Avelumab

Initial Indication:
• Treatment of pediatric and adult patients 12 years and older with metastatic Merkel cell carcinoma.

Subsequent Indication:
• Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Dose: 10mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.

Durvalumab (Imfinzi)

Disease included in current Indications per package insert:
• Urothelial cancer
• NSCLC (Feb 2018)

- Dose per package insert is 10 mg/kg IV over 60 minutes q 2 weeks
Durvalumab

- **Indications:**
  - **Bladder**: Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
  - **Lung Cancer**: Treatment of patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation.

  - **Dose:** durvalumab 10 mg/kg IV over 60 min q 2 weeks until disease progression or unacceptable toxicity.

There are still many remaining questions...

Dual Checkpoint Blockade?

Dual Checkpoint Inhibition

• CTLA-4 and PD-1 have distinct roles in regulating adaptive immunity.
• Dual checkpoint inhibition → synergistic activity

Melanoma: Nivolumab + Ipilimumab

• Method:
  • Double-blind study in patients with metastatic melanoma who had not previously received treatment
  • Patients randomly assigned in 2:1 ratio:
    • ipilimumab 3 mg/kg IV q3 wk x 4 doses + nivolumab 1 mg/kg q 3 wk x 4 →
    • nivolumab 3 mg/kg q 2 wk until disease progression or unacceptable toxicity
    • ipilimumab 3 mg/kg IV q3 wk x 4 doses + placebo q 3 wk x 4 → placebo q 2 wk
  • Endpoint:
    • Rate of investigator assessed, confirmed objective response

Melanoma: Nivolumab + Ipilimumab

• Results:
  • Objective response in patients with BRAF WT tumors
    • Ipilimumab + nivolumab: 63%
    • Ipilimumab + placebo: 11%
  • CR was seen in 22% in the combination arm

Melanoma: Nivolumab + Ipilimumab


Question

- Role of immune checkpoint inhibition and chemotherapy?

Advanced, non-squamous NSCLC (KEYNOTE-021): Carboptatin + pemetrexed + pembrolizumab

Methods:
- Randomized, open-label, phase II cohort of multicohort study (n=123)
- Pts stage IIIB or IV non-squamous NSCLC (chemotherapy naïve)
- Regimen:
  - Pembrolizumab 200 mg IV q 3 wk x 4 → 24 months or placebo
  - Carboplatin (AUC = 5) IV q 3 x 4
  - Pemetrexed 500 mg/m2 IV q 3 weeks → indefinite pemetrexed maintenance

Findings:
- Increase objective response to chemotherapy + pembrolizumab vs chemotherapy (estimated treatment difference of 26%)
- Incidence of grade 3 or worse treatment related adverse effects similar

Impact:
- Change in package insert
- Inclusion in NCCN guidelines for NSCLC

Question

• What is the place in therapy for immune checkpoint inhibition?

Durvalumab: Stage III NSCLC

• PACIFIC Trial: Phase III placebo controlled trials (n=709)
• Interim analysis
• Patient Population:
  - Individuals with locally advanced, unresectable stage III NSCLC
• Methods:
  - Patients randomly assigned 2:1 to durvalumab or placebo q 2 weeks for up to 12 months following chemoradiation (1 to 42 days) between 5/2014 – 5/2016
  - Primary endpoints: PFS and OS
  - Secondary endpoints: 12 month PFS, 18 month PFS, ORR, DOR, time to death or distant metastasis, safety
• Results:
  - Increased median PFS in treatment group
  - Increase in ORR in treatment group
  - Increase DOR in treatment group
  - Increase time to death in treatment group

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab (N=476)</th>
<th>Placebo (N=237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>16.8 mo</td>
<td>5.6 mo</td>
</tr>
<tr>
<td>12 month PFS</td>
<td>55.9%</td>
<td>35.9%</td>
</tr>
<tr>
<td>18 month PFS</td>
<td>44.2%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Median TT death / mets dz</td>
<td>23.2 mo</td>
<td>14.6 mo</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>16.5%</td>
<td>27.7%</td>
</tr>
</tbody>
</table>

Durvalumab: Stage III NSCLC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Durvalumab (N=443)</th>
<th>Placebo (N=213)</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>28.4%</td>
<td>16%</td>
<td>1.78 (95% CI, p &lt;0.001)</td>
</tr>
<tr>
<td>Median DOR</td>
<td>NR</td>
<td>13.8 months</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Objective Response Rate at data cutoff point (calculated Kaplan Meier method)

- RR at 12 mo: 72.8% vs 56.1%
- RR at 18 mo: 72.8% vs 46.8%


Durvalumab: Stage III NSCLC

- Among patients with locally advanced, unresectable NSCLC, PFS was 11 months longer among patients who received durvalumab vs placebo.
  - Responses were durable
  - Responses irrespective of baseline expression of PD-L1 on tumor cells
  - Durvalumab had a favorable effect on frequency of new metastases, including lower incidence of new brain metastases.
- Difference in PFS was seen across all prespecified groups
- Data on OS was immature at time of analysis
- Safety profile of durvalumab was consistent with other immune checkpoint inhibitors
  - Increased incidence of pneumonitis / radiation pneumonitis in both durvalumab and placebo group.

Durvalumab (Imfinzi)

- Expanded Indication (Feb 2018)

Question

- Role of immune checkpoint inhibition and targeted therapy?

Breakthrough Therapy Designation: Combination in Renal Cell Carcinoma

Strategy: multiple receptor TKI + immune checkpoint inhibitor

Clinical Trials:

Phase I
- Multicenter, open-label I/II clinical trial that evaluated the efficacy and safety of lenvatinib + pembrotilumab in patients with unresectable solid tumors who had disease progression after treatment with approved therapies
  - Primary objective: determine MTD

Phase II
- Combination therapy in patients who had select solid tumors with 0-2 prior lines of systemic therapy: lenvatinib 20 mg po daily + pembrolizumab 200 mg IV q 3 weeks
  - Primary objective: Objective response rates at 24 weeks
Question:

• Role of immune checkpoint inhibition and targeted therapy?

Immune Checkpoint Inhibitors + PARP Inhibition

Rationale:
• Preclinical studies demonstrated DNA damage promotes neoantigens expression.
• Oral poly (ADP-ribose) polymerase – inhibitors increase DNA damage.
• Potential that increase DNA damage with PARP inhibitors could increase mutational burden and expand neoantigens expression leading to greater immune recognition by the tumor.

Clinical trial:
• Phase I: Combination of durvalumab + PARP inhibitor and combination of durvalumab + VEGF inhibitor

Question:

• Role of immune checkpoint inhibition and vaccine therapy?

Question:

• Role of immune checkpoint inhibition and radiation therapy?

Methods:

• Multicenter, international, prospective, single-group, open-label, phase 2 trial (33 centers in North America, Europe, Australia, Asia)
• Pts (≥18 yrs) with stage IV chemotherapy-refractory Merkel Cell Cancer
• Key eligibility: PS 0–1, measurable disease RECIST, immune-competent status
• Tumor selection not based on PD-L1 expression or Merkel cell polyomavirus status

Treatment:

• Avelumab 10 mg/kg q 2 wks IV over 1 hr until confirmed disease progression, unacceptable toxicity or occurrence of other criteria for withdrawal.
• Pts with confirmed CR treated for minimum of 6 months and maximum of 12 months after confirmation.
• Treatment beyond 12 months was allowed on the basis of investigator assessment of potential benefit.
• Pts could stay on treatment beyond observation of progressive disease provided there was not significant clinical deterioration or change in PS to ≤2 or before the limit more than 14 days.

Question:
• Patient selection for immune checkpoint inhibitors?

Question:
• How safe are immune checkpoint inhibitors in therapy?

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Typical Timing of Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic (rash, pruritis, vitiligo)</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Gastrointestinal (diarrhea, colitis)</td>
<td>5-6 weeks</td>
</tr>
<tr>
<td>Hepatic (elevated ALT, elevated AST)</td>
<td>7-10 weeks</td>
</tr>
<tr>
<td>Endocrine (hypothyroidism, hyperthyroidism, hypophysitis)</td>
<td>7-10 weeks</td>
</tr>
<tr>
<td>Pulmonary (pneumonitis)</td>
<td>unknown</td>
</tr>
<tr>
<td>Neurologic (neuropathy, arthralgia, myalgia)</td>
<td>unknown</td>
</tr>
</tbody>
</table>

* melanoma

Rubin KM. CJON 2015;19:709-717
Immune Checkpoint Inhibition: Adverse Events

Immune Checkpoint Inhibitor and Immunotherapy: Adverse Effects

• Reimschissel E, et al. Immunotherapy toxicities: A new electronic documentation template to improve patient care. pg 43-44
Society for Immunotherapy of Cancer (SITC)

Guidelines for Managing Toxicities with Immune Checkpoint Inhibitors

• NCCN Guideline (2018)
ASCO Guidelines: Recommendations

- Patient and family caregivers should receive timely and timely education about immunotherapies, their mechanism of action, and the clinical profile of possible adverse events prior to initiating therapy and throughout treatment and survivorship.
- There should be a high level of suspicion that new symptoms are treatment related.
- In general, ICI therapy should be continued with close monitoring for grade 1 toxicities, with the exception of some neurologic, hematologic, and cardiac toxicities.
- Hold ICIs for most grade 2 toxicities and consider reinitiating when symptoms and/or laboratory values revert to grade 1 or less. Corticosteroids (initial dose of 0.5 to 1 mg/kg of prednisone or equivalent) may be administered.
- Hold ICIs for grade 3 toxicities and consider high-dose corticosteroids (prednisone 1-2 mg/kg/day or methylprednisolone 4 to 6 mg/kg day). Corticosteroids should be tapered over the course of at least 3 to 6 weeks. If symptoms do not improve with 48 to 72 hours of high-dose corticosteroids, infliximab may be offered for some toxicities.
- When symptoms and/or laboratory values revert to grade 1 or less, rechallenging with ICIs may be offered, however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended.
- In general, grade 3 toxicities warrant permanent discontinuation of ICIs, with the exception of endocrinopathies that have been controlled by hormone replacement.


Immune-Related Adverse Effects

- Mechanism: infiltration of normal tissue by activated T cells responsible for autoimmunity
  - Tissues:
    - Skin
    - Gastrointestinal tract
    - Endocrine glands
    - Lung
    - Nervous system
    - Liver
    - Kidney
    - Hematological cells
    - Musculo-tendinous system
    - Heart
    - Eyes

The challenge of diarrhea with ICI

- Differential: diarrhea vs colitis
- Presentation:
  - Frequent, watery bowel movements
  - Abdominal cramping
  - Blood or mucus in stool
  - Incidental finding on imaging
- Assessment:
  - Review of symptom (duration, onset, self-management strategies)
  - Review of bowel patterns
  - Review of diet
  - Review of medications
**Toxicity Grading: Diarrhea and Colitis**

![Toxicity Grading Table]

*Common Toxicity Terminology Criteria for Adverse Events v 4.03, NCI CTEP, 2010*

---

**Immune Checkpoint Inhibitor Colitis**

<table>
<thead>
<tr>
<th>Diarrhea Management</th>
<th>Colitis Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid</td>
<td>Treatment delays</td>
</tr>
<tr>
<td>Diet</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Antidiarrheals</td>
<td></td>
</tr>
<tr>
<td>Medication optimization</td>
<td></td>
</tr>
</tbody>
</table>

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**Immune Checkpoint Inhibitors: irAE**

ENDOCRINE GLAND toxicities include:
- Hypo- or hyperthyroidism, thyroiditis
- Hypophysitis (inflammation of the pituitary gland)
- Adrenal insufficiency
- Diabetes

References:
Immune Checkpoint Inhibitors: Thyroid

- Incidence: Incidence does not appear to be the same for all immune checkpoint inhibitors, but does appear to increase with combination immune checkpoint inhibitor.
- Pathogenesis: It is thought due to destructive thyroiditis mediated by cytotoxic T cells against the thyroid gland.
- Presentation: Can vary among patients:
  - With monitoring increase in TSH may proceed symptoms
  - Cases have been reported of thyroid storm or severe hypothyroidism
- Monitoring: TSH, free T4, assessment of pituitary, adrenal, gonadal functional status
- Management is dependent on diagnosis:
  - Hypothyroidism → thyroid replacement
  - Thyrotoxicosis → beta blockers may be required (control symptoms)

Incidence of Thyroid Disease with Immune Checkpoint Inhibitors


Immune Checkpoint Inhibitors: Pituitary Gland

Hypophysitis

- Incidence does not appear to be the same for all immune checkpoint inhibitors, but does appear to increase with combination immune checkpoint inhibitor.
- Dose related for CTLA-4 inhibitor ipilimumab?
- Pathogenesis → autoimmune based mechanism
  - Presentation:
    - Panhypopituitarism
    - Isolated anterior pituitary hormone deficiency
    - Pituitary enlargement
- Monitoring: TSH, free T4
- Management is dependent on diagnosis


Care of the Individual on Chronic Physiologic Corticosteroids

- Long-term corticosteroid and mineralocorticoid replacement is often required
- Provide patient AND caregiver with instructions (oral and written):
  - Advising all caregivers and healthcare team members of therapy
  - Instructions for increasing corticosteroid doses in situations of acute illness, stress or medical procedures.
  - Medical alert bracelet
  - Identification card
  - Emergency hydrocortisone IM injection kit
Immune Checkpoint Inhibitors: Hepatotoxicity

Retrospective observational study in individuals with melanoma treated between March 2011 – March 2016 that were treated with ipilimumab, nivolumab, pembrolizumab or combination ipilimumab + nivolumab.

• Hepatotoxicity → increased LFTs and bilirubin
• Onset of hepatotoxicity: median time from first dose 52 days
• Clinical presentation: variable, including concurrent other sAE
• Management: steroids, discontinuation of therapy (most), additional immunosuppression


Avelumab: Merkel Cell Carcinoma

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Grade 1-2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>24%</td>
<td>0</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>17%</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9%</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>7%</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Mucosal rash</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

Possible immune mediated AE

Hypothyroidism          | 3%       | 0       |
Hyperthyroidism         | 2%       | 0       |
Pneumonitis             | 1%       | 0       |
Type 1 diabetes mellitus | 1%    | 0       |


Immune Checkpoint Inhibitors: Fatigue

• Fatigue is one of the most frequent adverse effect of immune checkpoint inhibitors
• Meta-analysis evaluated fatigue in 17 clinical trials with ipilimumab, pembrolizumab, nivolumab and tremelimumab
  - Incidence of all grade treatment-associated fatigue ranges from 14 – 42%
  - Incidence of high grade treatment-associated fatigue varied from 1 – 11%
  - Incidence dependent on a variety of issues including:
    - Agent
    - Dose
    - Scheduled
    - Combination vs single agent

Anticipating and recognizing potential obstacles…

Immune Checkpoint Inhibition Strategies
- Cytotoxic T Lymphocyte Antigen 4 inhibition:
  - Ipilimumab
- PD-1 inhibition:
  - Nivolumab
  - Pembrolizumab
- PD-L1 inhibition:
  - Atezolizumab
  - Avelumab
  - Durvalumab
- Combination therapy:
  - Ipilimumab + nivolumab
  - Chemotherapy + immunotherapy: carboplatin + pemetrexed + pembrolizumab
  - Chemotherapy followed by immunotherapy: chemoradiation + durvalumab
  - Targeted therapy + immune checkpoint inhibitors

Question
- Are these agents “cost effective”?
Considerations for Cost of Care Discussion

- Cost of immunotherapy
- Single agent
- Combination
- Place in therapy
- Duration of therapy
- Cost associated with management of immunotherapy complications
  - Prevention
  - Management
  - Cost of alternatives...

Target: CD19 on B cell
Strategy: Genetically Modified T Cell

Cell Surface Antigens on B Cell
Tisagenlecleucel (Kymriah)

- CD19-directed genetically modified autologous T cell immunotherapy
- Autologous T cells from patients peripheral mononuclear cells (leukaphereses)
- Genetically modified using lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR)
- CAR is fused to intracellular signaling domains that activate T cells and enhance response

Goal: Reprogramming a patients own T cells to identify and eliminate CD-19 expressing cells (normal cells + malignant cells)
Tisagenlecleucel: ALL

Methods:
• Phase II, single-cohort, 25 center, global study
• Pediatric and young adult patients with CD19+ relapsed or refractory B-cell ALL (n=75)
• Primary endpoint: overall remission rate within 3 months

Results:
• Overall remission rate within 3 months: 81%
• Event-free survival: 73% (6 months) → 50% (12 months)
• Overall survival: 90% (6 months) → 76% (12 months)
• Persistence of tisagenlecleucel in blood was observed for “as long as 20 months”


---

<table>
<thead>
<tr>
<th>Safety Event</th>
<th>Any Time (n=75)</th>
<th>≤ 8 week after infusion (n=75)</th>
<th>&gt; 8 week to 1 year after infusion (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event (any grade)</td>
<td>100%</td>
<td>99%</td>
<td>93%</td>
</tr>
<tr>
<td>Adverse event believed to be attributed to tisagenlecleucel</td>
<td>95%</td>
<td>92%</td>
<td>43%</td>
</tr>
<tr>
<td>Adverse event Grade 3 or 4</td>
<td>88%</td>
<td>83%</td>
<td>44%</td>
</tr>
<tr>
<td>Adverse event Grade 3 or 4 Believed to be attributed to tisagenlecleucel</td>
<td>73%</td>
<td>69%</td>
<td>17%</td>
</tr>
</tbody>
</table>


---

<table>
<thead>
<tr>
<th>Selected Adverse Events seen within 8 Weeks after tisagenlecleucel infusion</th>
<th>Any Grade (n=75)</th>
<th>Grade 3 (n=75)</th>
<th>Grade 4 (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>77%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>40%</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>Infection</td>
<td>43%</td>
<td>21%</td>
<td>3%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>35%</td>
<td>32%</td>
<td>3%</td>
</tr>
<tr>
<td>Cytokine NOT resolving by day 28</td>
<td>37%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>4%</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Tisagenlecleucel (Kymriah)

- Current indication:
  - Treatment of patients up to 25 years with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse
- Warnings → restricted program
  - Cytokine release syndrome (CRS)
  - Neurologic toxicities
  - Infections
  - Prolonged cytopenias
  - Hypogammaglobulinemia
  - Secondary malignancy

CD19-specific CAR T cells: Follow-up

- Methods:
  - Phase 1 trial in adults with relapsed ALL from MSKCC
  - Safety and long term outcomes in 53 adults
- Results:
  - After infusion: CRS in 26% (one death)
  - CR in 83% patients
  - Median follow-up of 29 months:
    - Median event-free survival was 12.9 months (95% CI, 8.7 – 23.4)
    - Patients with low disease burden prior to treatment had increased remission duration and survival
    - Patients with higher disease burden prior to treatment had increased CRS and neurologic toxicity and shorter long-term survival.

Axicabtagene ciloleucel (Yescarta)

- Chimeric antigen receptor T cell immunotherapy
  - Autologous T cells genetically modified to produce a CAR protein
  - CAR T cells identify and eliminate CD19-expressing normal and malignant cells
- Indication:
  - Treatment of adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy
  - Diffuse large B-cell lymphoma (DLBCL)
  - Primary mediastinal large B-cell lymphoma
  - High-grade B-cell lymphoma
  - DLBCL arising from follicular lymphoma
Axicabtagene Ciloleucel CAR T-Cell in Refractory Large B-Cell Lymphoma

**Methods:**
- Multicenter Phase 2 trial (n=111)
- Pts with DLBCL, primary mediastinal B-cell lymphoma, transformed follicular lymphoma (refractory disease)
- Target dose of 2 x 10^6 anti-CD19 CAR T cells per kg (after conditioning regimen of low-dose cyclophosphamide + fludarabine)
- Primary endpoint: ORR

**Results**
- Axicabtagene ciloleucel was successfully manufactured for 99% pts, administered to 91%
- ORR: 82%
- CR rate: 54%
- OS at 18 months: 52%
- Most common adverse effects (grade 3 or higher): neutropenia (78%), anemia (43%), thrombocytopenia (18%) CR (grade 3 or higher): 13%
- Neurologic events: 28%


What are biosimilars?

"Biosimilars are a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components.

There are no clinically meaningful differences between the biological product and the reference product in terms of safety, efficacy, purity and potency of the product."

FDA Guidance 2012

**Definition of a Biologic**

- Biologics were first developed in the 1980s using recombinant DNA technology.
- Biologic products include a wide range of products.
- US Federal Code of Regulation defines biologic as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of disease or injuries of man.

**Biologics vs. Small Molecules**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Conventional Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Product</td>
<td>Chemical-based</td>
<td>Protein-based</td>
</tr>
<tr>
<td>Structure</td>
<td>Simple</td>
<td>Complex</td>
</tr>
<tr>
<td>Stability</td>
<td>Stable</td>
<td>Unstable</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>• Defined, reproducible chemical process • Identical copies can be made.</td>
<td>• Unique biological processes within living cell lines • Impossible to ensure identical copies.</td>
</tr>
<tr>
<td>Characterization</td>
<td>Easy to fully characterize</td>
<td>Difficult to characterize fully due to a mixture of related molecules</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Non-immunogenic</td>
<td>Immunogenic</td>
</tr>
</tbody>
</table>

When is a biologic not a biosimilars?

- Biologics that are licensed as an innovator molecule are not called biosimilars.
- Tbo-filgrastim (Granix®) is licensed in the US as an innovator molecule and is not (considered) a biosimilar in the US.
- Tbo-filgrastim is licensed in other countries and is considered a biosimilar in those countries (and in the literature)

**Biosimilar is a regulatory term in the US.**